



Health  
Canada

Santé  
Canada

Your health and  
safety... our priority.

Votre santé et votre  
sécurité... notre priorité.

Proposed Registration Decision

PRD2014-20

# Flupyradifurone

*(publié aussi en français)*

**19 September 2014**

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications  
Pest Management Regulatory Agency  
Health Canada  
2720 Riverside Drive  
A.L. 6604-E2  
Ottawa, Ontario K1A 0K9

Internet: [pmra.publications@hc-sc.gc.ca](mailto:pmra.publications@hc-sc.gc.ca)  
[healthcanada.gc.ca/pmra](http://healthcanada.gc.ca/pmra)  
Facsimile: 613-736-3758  
Information Service:  
1-800-267-6315 or 613-736-3799  
[pmra.infoserv@hc-sc.gc.ca](mailto:pmra.infoserv@hc-sc.gc.ca)

**Canada**

ISSN: 1925-0878 (print)  
1925-0886 (online)

Catalogue number: H113-9/2014-20E (print version)  
H113-9/2014-20E-PDF (PDF version)

**© Her Majesty the Queen in Right of Canada, represented by the Minister of Health Canada, 2014**

All rights reserved. No part of this information (publication or product) may be reproduced or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, or stored in a retrieval system, without prior written permission of the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5.



## Table of Contents

Overview .....	1
Proposed Registration Decision for Flupyradifurone .....	1
What Does Health Canada Consider When Making a Registration Decision? .....	1
What Is Flupyradifurone? .....	2
Health Considerations .....	2
Environmental Considerations .....	5
Measures to Minimize Risk .....	7
Next Steps .....	8
Other Information .....	8
Science Evaluation .....	9
1.0 The Active Ingredient, Its Properties and Uses .....	9
1.1 Identity of the Active Ingredient .....	9
1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product .....	10
1.3 Directions for Use .....	11
1.4 Mode of Action .....	12
2.0 Methods of Analysis .....	12
2.1 Methods for Analysis of the Active Ingredient .....	12
2.2 Method for Formulation Analysis .....	12
2.3 Methods for Residue Analysis .....	12
3.0 Impact on Human and Animal Health .....	13
3.1 Toxicology Summary .....	13
3.1.1 Pest Control Products Act Hazard Characterization .....	20
3.2 Acute Reference Dose (ARfD) .....	21
3.3 Acceptable Daily Intake (ADI) .....	22
3.4 Occupational Risk Assessment .....	22
3.4.1 Toxicological Endpoints for Occupational Exposure Assessments .....	22
3.4.2 Occupational Exposure and Risk .....	25
3.4.3 Residential Exposure and Risk Assessment .....	28
3.5 Food Residues Exposure Assessment .....	28
3.5.1 Exposure from Drinking Water .....	28
3.5.2 Residues in Plant and Animal Foodstuffs .....	29
3.5.3 Dietary Risk Assessment .....	30
3.5.4 Aggregate Exposure and Risk .....	31
3.5.5 Maximum Residue Limits .....	31
4.0 Impact on the Environment .....	33
4.1 Fate and Behaviour in the Environment .....	33
4.2 Environmental Risk Characterization .....	34
4.2.1 Risks to Terrestrial Organisms .....	35
4.2.2 Risks to Aquatic Organisms .....	42
4.2.3 Incident Reports .....	46
5.0 Value .....	46
5.1 Effectiveness Against Pests .....	46
5.2 Phytotoxicity to Host Plants .....	47
5.3 Economics .....	47

5.4	Sustainability .....	47
5.4.1	Survey of Alternatives .....	47
5.4.2	Compatibility with Current Management Practices Including Integrated Pest Management.....	47
5.4.3	Information on the Occurrence or Possible Occurrence of the Development of Resistance .....	47
5.4.4	Contribution to Risk Reduction and Sustainability .....	48
6.0	Pest Control Product Policy Considerations.....	48
6.1	Toxic Substances Management Policy Considerations.....	48
6.2	Formulants and Contaminants of Health or Environmental Concern .....	49
7.0	Summary .....	49
7.1	Human Health and Safety .....	49
7.2	Environmental Risk.....	51
7.3	Value .....	52
8.0	Proposed Regulatory Decision.....	52
	List of Abbreviations .....	53
Appendix I	Tables and Figures .....	63
Table 1	Residue Analysis.....	63
Table 2	Toxicity Profile of End-use Products Containing Flupyradifurone.....	64
Table 3	Toxicity Profile of Flupyradifurone.....	65
Table 4	Toxicity Profile of Flupyradifurone Metabolites.....	71
Table 5	Toxicology Endpoints for Use in Health Risk Assessment for Flupyradifurone ...	74
Table 6	Exposure & risk estimates for workers in commercial seed treatment facilities treating soybeans with BYI 02960 480 FS .....	75
Table 7	Mixer/loader/applicator exposure and risk to flupyradifurone from Sivanto 200 SL.....	75
Table 8	Exposure & risk estimates from planting soybeans seeds treated commercially with BYI 02960 480 FS .....	76
Table 9	Integrated Food Residue Chemistry Summary .....	76
Table 10	Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment	94
Table 11	Postapplication risk assessment for flupyradifurone (shading indicates target MOE not exceeded) .....	96
Table 12	Summary of fate and behaviour of flupyradifurone in the environment .....	97
Table 13	Summary of EECs used for screen level risk assessment.....	99
Table 14	Effects of flupyradifurone on terrestrial organisms (excluding bees) .....	99
Table 15	Effects of flupyradifurone, Sivanto 200 SL and BYI 02960 480 FS formulations and the transformation products on bees. ....	102
Table 16	Effects of flupyradifurone on aquatic organisms.....	103
Table 17	Risk to soil dwelling organisms as a result of direct in-field and off-field exposure	105
Table 18	Risk assessment to foliar-dwelling organisms as a result of in-field and off-field exposure .....	106
Table 19	Refinement to the risk to foliar-dwelling and soil-dwelling organisms from in-field and off-field exposure. ....	107
Table 20	Details of results from the semi-field and field studies .....	107

Table 21	Screening Level EECs and RQ values for honeybees based on foliar, drench, and seed treatment applications.....	108
Table 22	Risk to different castes of bees based on maximum residues of flupyradifurone (mg a.i./kg) in various matrices following soil drench and foliar applications to different crops.....	109
Table 23	Tier II and III Semi-field Colony-Level Bee Toxicity Studies.....	110
Table 24	Risk to birds and mammals as a result of direct on-field and off-field exposure after a single soil application of 400 g a.i./ha.....	114
Table 25	Risk to birds and mammals as a result of direct on-field and off-field exposure after foliar application at 2 × 200 g a.i./ha with a 7-day interval.....	116
Table 26	Risk assessment for birds and mammals consuming flupyradifurone treated soybean seeds.....	118
Table 27	Risk assessment of BYI 02960 SL 200 to non-target terrestrial vascular plants at a single application of 400 g a.i./ha.....	119
Table 28	Screening level risk to aquatic organisms.....	119
Table 29	Refined risk assessment of BYI 02960 SL 200 to non-target aquatic organisms via spray drift to an 80 cm deep water body.....	120
Table 30	Refined risk assessment of BYI 02960 SL 200 to non-target aquatic organisms via run-off and pore water in an 80 cm deep water body.....	120
Table 31	Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria.....	120
Table 32	Uses of SIVANTO 200 SL (maximum rate/crop/year is 400 g flupyradifurone/ha).....	121
Table 33	Uses of BYI 02960 480 FS (maximum rate/crop/year is 400 g flupyradifurone/ha).....	122
Appendix II	Supplemental Maximum Residue Limit Information—International Situation and Trade Implications.....	123
Table 1	Comparison of Canadian MRLs, and American Tolerances.....	123
References	.....	125



## Overview

### Proposed Registration Decision for Flupyradifurone

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Flupyradifurone TC, and the end-use products BYI 02960 480 FS and Sivanto 200 SL, containing the technical grade active ingredient flupyradifurone, to control various insect pests.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Flupyradifurone TC, BYI 02960 480 FS and Sivanto 200 SL.

### What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable<sup>1</sup> if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value<sup>2</sup> when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at [healthcanada.gc.ca/pmra](http://healthcanada.gc.ca/pmra).

---

<sup>1</sup> "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

<sup>2</sup> "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on flupyradifurone, the PMRA will consider all comments received from the public in response to this consultation document.<sup>3</sup> The PMRA will then publish a Registration Decision<sup>4</sup> on flupyradifurone, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

## **What Is Flupyradifurone?**

Flupyradifurone is an insecticide in a new Mode of Action (MoA) Subgroup (Subgroup 4D, the Butenolides), that interferes with the function of insect nerves. MoA Group 4 includes the neonicotoids (4A), nicotine (4B) and sulfoxaflor (4C). Flupyradifurone is active by ingestion and contact, but is more potent via ingestion. This active ingredient is systemic when applied as a soil treatment and has translaminar activity when applied as a foliar treatment. Formulated as BYI 02960 480 FS and used to treat soybean seeds, it controls soybean aphids and adult bean leaf beetles. Formulated as Sivanto 200 SL and sprayed on the foliage of various field, vegetable, fruit and nut crops (for example, leafy vegetables, legumes, fruiting vegetables, cucurbits, pome fruit, berries, tree nuts, corn, alfalfa, peanut and hops), flupyradifurone controls aphids, leafhoppers, scale insects, whiteflies, Colorado potato beetle, and blueberry maggot and suppresses pear psylla. When applied as a soil application to fruiting vegetables, cucurbits and berries and small fruits, Sivanto 200 SL controls aphids, leafhopper and whiteflies. This product can be applied by air to tuberous, corm, root and legume vegetables.

## **Health Considerations**

### **Can Approved Uses of Flupyradifurone Affect Human Health?**

**Products containing flupyradifurone are unlikely to affect your health when used according to label directions.**

Potential exposure to flupyradifurone may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

---

<sup>3</sup> "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

<sup>4</sup> "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.



Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, flupyradifurone was slightly acutely toxic via the oral route; therefore the signal word and hazard statement "CAUTION – POISON" are required on the label. Flupyradifurone was demonstrated to be of low acute toxicity via the dermal and inhalation routes, non-irritating to skin, and minimally irritating to eyes. The potential for flupyradifurone to cause an allergic skin reaction could not be ruled out based on the information provided; therefore, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label for the active ingredient.

Sivanto 200 SL, the end-use product for foliar and soil treatment containing flupyradifurone, was demonstrated to be of low acute toxicity via the oral, dermal and inhalation routes. It was determined to be non-irritating to the skin and minimally irritating to the eye. Sivanto 200 SL did cause an allergic skin reaction; therefore, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label for this end-use product.

BYI 02960 480 FS, the end-use product for seed treatment containing flupyradifurone, was demonstrated to be slightly acutely toxic via the oral route; therefore the signal word and hazard statement "CAUTION – POISON" are required on the label. BYI 02960 480 FS was determined to be of low acute toxicity via the dermal and inhalation routes, minimally irritating to the skin and non-irritating to the eye, and did not cause an allergic skin reaction.

Flupyradifurone did not cause cancer in animals and did not damage genetic material. There was no indication that flupyradifurone caused damage to the immune system. Health effects in animals given repeated doses of flupyradifurone included effects on the liver, thyroid gland, kidney, and skeletal muscle. Effects on reproduction were observed at high doses.

When flupyradifurone was given to pregnant animals, an effect of a serious nature was observed in the developing fetus (death) at a dose that was toxic to the mother.

The risk assessment protects against the effects of flupyradifurone by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

## **Residues in Water and Food**

### **Dietary risks from food and drinking water are not of health concern.**

Refined aggregate dietary intake estimates (food plus drinking water) revealed that children 1 to 2 years of age, the highest exposed subpopulation, are expected to be exposed to less than 31% of the acceptable daily intake (ADI). Based on these estimates, the refined chronic dietary risk from flupyradifurone is not of health concern for all population subgroups.

Flupyradifurone is not genotoxic or carcinogenic; therefore, a cancer dietary risk assessment is not required.

Refined acute dietary (food plus drinking water) intake estimate was less than 26% of the acute reference dose for children 1 to 2 years of age, the highest exposed subpopulation. The refined aggregate exposure from food and drinking water is considered acceptable for females 13 to 49 years of age at 24% of the acute reference dose (ARfD).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada, the United States, and Brazil (coffee) using flupyradifurone on a range of representative commodities were deemed acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of this consultation document.

### **Risks in Residential and Other Non-Occupational Environments**

Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings. Therefore, bystander exposure is expected to be minimal.

The occupational re-entry worker exposure to treated crops was not of concern and is expected to address any potential exposure to bystanders in a pick-your-own (PYO) scenario.

### **Occupational Risks From Handling Flupyradifurone**

**Occupational risks are not of concern when flupyradifurone is used according to the proposed label directions, which include protective measures.**

Workers in commercial seed treatment facilities (and mobile treaters) and farmers handling seed treated with BYI 02960 480 FS can come into direct contact with flupyradifurone through residues on the skin and through inhaling dust. Therefore, the label states that workers in commercial seed treatment facilities (and mobile treaters) must wear coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, goggles, and shoes plus socks. Treaters and baggers/sewers/stackers must wear a NIOSH approved respirator. Soybean seeds can only be treated in closed treatment systems. Farmers planting and handling treated seed must wear long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks. Planters must use a closed cab tractor.

Farmers and custom applicators who mix, load and apply Sivanto 200 SL as a foliar or soil treatment and field workers re-entering treated fields can come in direct contact with flupyradifurone residues on the skin and/or through inhalation. Therefore, the label specifies that

anyone mixing/loading and applying flupyradifurone must wear long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks. The label also requires that workers not enter treated fields for 12 hours after application except for hand girdling of table grapes where workers cannot re-enter for 24 hours.

Taking into consideration these label statements, precautionary measures, and the exposure duration for handlers and workers, it was determined that the risks to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

## **Environmental Considerations**

### **What Happens When Flupyradifurone Is Introduced Into the Environment?**

**Flupyradifurone may pose a risk to bees, non-target beneficial arthropods, and freshwater and saltwater invertebrates when used for foliar application. Flupyradifurone may pose a risk to birds and small wild mammals when used for soybean seed treatment.**

Flupyradifurone can enter the environment when it is used as an insecticide for control of a large number of pests in a variety of crops. It can be applied as a foliar spray, as a soil drench and as a seed treatment. Flupyradifurone is systemic and, therefore, can reach pollen and nectar through its movement inside the plant.

In the terrestrial environment in Canada, flupyradifurone can persist in the environment and has a potential to carryover to the following growing season. Breakdown of the molecule is predominantly by soil microbes which produce two major transformation products, 6-chloronictinic acid (6-CNA) and difluoroacetic acid (DFA). 6-CNA breaks down rapidly while DFA can persist in soil. Flupyradifurone does not readily break down by reacting with water or sunlight. Flupyradifurone is not volatile and unlikely to enter the atmosphere. Flupyradifurone and the transformation product DFA have the potential to move through the soil to enter groundwater. Flupyradifurone and DFA also have the potential to enter aquatic environment through surface run-off.

In the aquatic environment, flupyradifurone does not break down readily in the presence of microbes or by reacting with water. However, it can break down by reacting with sunlight in water where light can penetrate, producing two major transformation products: BYI 02960-succinamide and azabicyclosuccinamide. By and large, once flupyradifurone enters the aquatic environment, particularly turbid waters, it may persist for a long time.

Flupyradifurone is not expected to appreciably accumulate in fish tissues.



Overall, flupyradifurone and its major transformation products present a negligible risk to soil dwelling organisms, terrestrial and aquatic plants, freshwater algae, fish (freshwater and marine), and amphibians. However, flupyradifurone may affect some species of aquatic invertebrates from soil and foliar applications. Flupyradifurone may also affect beneficial arthropods and bees from foliar applications.

Flupyradifurone may pose a risk to birds and small wild mammals when used for soybean seed treatment.

In order to minimize the potential risk of flupyradifurone to terrestrial and aquatic organisms, precautionary label statements as well as mitigation measures are specified on the labels of the end use products (refer to the Measures to Minimize Risk Section below).

## **Value Considerations**

### **What Is the Value of BYI 02960 480 FS?**

**Applied to soybean seeds, BYI 02960 480 FS provides early season protection of seedlings against soybean aphids and adult bean leaf beetles.**

BYI 02960 480 FS provides a new MoA Subgroup (Subgroup 4D, the Butenolides) for early season protection of soybean seedlings against soybean aphid and adult bean leaf beetles. Soybean aphids and bean leaf beetles are major pests of soybean. Other MoA Group 4 active ingredients are registered for use on soybean against these pests.

### **What Is the Value of Sivanto 200 SL?**

**Sprayed on a variety of outdoor crops, Sivanto 200 SL controls aphids, leafhoppers, scale insects, whiteflies, Colorado potato beetle, and blueberry maggot and suppresses pear psylla. Applied as a soil treatment to fruiting vegetables, cucurbits, and berries and small fruit, Sivanto 200 SL controls aphids, leafhoppers and whiteflies.**

As a foliar application, Sivanto 200 SL controls several serious pests on a variety of outdoor crops. Pests which Sivanto 200 SL can be used against include whiteflies, an emerging pest of outdoor crops in Canada; aphids and leafhoppers, which are major pests of a variety of outdoor crops; scale insects, important pests of pome fruits which are considered difficult to control; blueberry maggot, an important pest of blueberries; Colorado potato beetle, an important pest of potato and fruiting vegetables; and pear psylla, an important pest of pear. Soil applications of Sivanto 200 SL to fruiting vegetables, cucurbits, and berries and small fruit control aphids, leafhoppers and whiteflies. Many of these pests have developed resistance to older chemistries. Sivanto 200 SL provides a new mode of action subgroup for use against these pests. Other MoA Group 4 active ingredients are registered for use on many of these crops and pests.

## **Measures to Minimize Risk**

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the labels of BYI 02960 480 FS and Sivanto 200 SL to address the potential risks identified in this assessment are as follows.

### **Key Risk-Reduction Measures**

#### **Human Health**

As direct contact with flupyradifurone on the skin or through inhalation of spray mists can occur, anyone mixing, loading and applying BYI 02960 480 FS in commercial seed treatment facilities (and mobile treaters) must use closed treatment systems only. Workers must wear coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, shoes plus socks and goggles. Treater/applicators and baggers/sewers/stackers must wear a NIOSH approved respirator. Workers planting and handling treated soybean seed on the farm must wear long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks and plant using a closed cab tractor.

Workers mixing, loading and applying Sivanto 200 SL as a foliar or soil application through ground application equipment or chemigation systems must wear long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks.

#### **Environment**

To mitigate potential exposure of aquatic organisms through spray drift, spray buffer zones of 1–10 metres are required to protect sensitive aquatic habitats and must be specified on the label of Sivanto 200 SL. Instructions for reducing run-off are required on the label of Sivanto 200 SL.

To mitigate the potential effects of flupyradifurone to bees, foliar applications are to be made in the early morning or evening when bees are not actively foraging, and measures to reduce drift are to be followed, as specified on the label of Sivanto 200 SL.

To mitigate the potential effects of flupyradifurone to beneficial arthropods, measures to reduce drift are required on the label of Sivanto 200 SL.

To minimize potential risk of flupyradifurone to birds and small wild mammals through ingestion of treated seeds, hazard statements are required on the label and on the tags of bags containing treated seeds. Guidance to reduce the availability (spills) of treated seeds and Best Management Practices are required on the label of BYI 02960 480 FS.



To minimize the potential of flupyradifurone and its transformation product difluoroacetic acid to enter groundwater, a label statement informing the users of the leaching potential of this chemical is to be specified on the label of Sivanto 200 SL.

To minimize the potential of flupyradifurone to be carried over to the following growing season, label statement informing the users of the carry-over potential of this chemical is to be specified on the label of Sivanto 200 SL.

## **Next Steps**

Before making a final registration decision on flupyradifurone, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

## **Other Information**

When the PMRA makes its registration decision, it will publish a Registration Decision on flupyradifurone (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

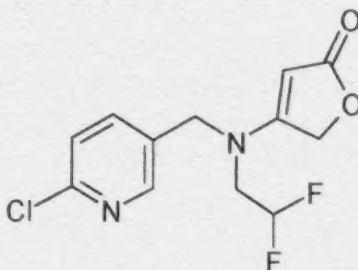
## Science Evaluation

### Flupyradifurone

#### 1.0 The Active Ingredient, Its Properties and Uses

##### 1.1 Identity of the Active Ingredient

Active substance	Flupyradifurone
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	4-{[(6-chloropyridin-3-yl)methyl](2,2-difluoroethyl)amino}furan-2(5 <i>H</i> )-one OR 4-[(6-chloro-3-pyridylmethyl)(2,2-difluoroethyl)amino]furan-2(5 <i>H</i> )-one
2. Chemical Abstracts Service (CAS)	4-[[[(6-chloro-3-pyridinyl)methyl](2,2-difluoroethyl)amino]-2(5 <i>H</i> )-furanone
CAS number	951659-40-8
Molecular formula	C <sub>12</sub> H <sub>11</sub> ClF <sub>2</sub> N <sub>2</sub> O <sub>2</sub>
Molecular weight	288.68
Structural formula	



Purity of the active ingredient	98.36%
---------------------------------	--------

## 1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

### Technical Product— Flupyradifurone Technical

Property	Result		
Colour and physical state	Beige to pink powder		
Odour	Distinct solvent-like odour		
Melting range	67.1°C		
Boiling point or range	Begins to decompose at 245°C		
Relative density	1.52		
Vapour pressure at 20°C	$9.1 \times 10^{-7}$ Pa		
Henry's law constant at 20°C	$8.2 \times 10^{-8}$ Pa $\times$ m <sup>3</sup> $\times$ mol <sup>-1</sup>		
Ultraviolet (UV)-visible spectrum	Medium	Peak maxima [ $\lambda$ , nm]	Molar absorptivity [1000 cm <sup>2</sup> /mol]
	Neutral methanol	213	9615.06
		259	25800.49
	pH 2 methanol	214	9388.74
		259	26576.75
	pH 10 methanol	213	9996.41
		259	25954.64
No peak maxima above 290 nm.			
Solubility in water at 20°C	3.2 g/L in distilled water		
Solubility in organic solvents at 20°C	solvent	[g/L]	
	methanol	> 250	
	n-heptane	0.0005	
	toluene	3.7	
	dichloromethane	> 250	
	acetone	> 250	
	ethyl acetate	> 250	
dimethyl sulfoxide	> 250		
<i>n</i> -Octanol-water partition coefficient ( <i>K</i> <sub>ow</sub> )	log <i>K</i> <sub>ow</sub> = 1.2 at pH 4, 7 and 9		
Dissociation constant (p <i>K</i> <sub>a</sub> )	No dissociation occurs in aqueous solutions in the pH range of 1 to 12.		
Stability (temperature, metal)	Stable to metals and metal ions, and at elevated temperature (54°C for 2 weeks).		

### End-use Products—BYI 02960 480 FS and Sivanto 200 SL

Property	Result for BYI 02960 480 FS	Result for Sivanto 200 SL
Colour	Beige	Clear brown to pink
Odour	Paint-like	Weak characteristic odour
Physical state	Liquid	Liquid
Formulation type	Suspension	Solution
Guarantee	480 g/L	200 g/L
Container material and description	HDPE bottles, 1–1000 L	
Relative density	1.189	1.174
pH of 1% dispersion in water	5.1	5.4
Oxidizing or reducing action	No oxidizing properties	No oxidizing properties
Storage stability	The active substance content was shown to be stable for 1 year at ambient temperature (mean 22.9°C) stored in HDPE.	The active substance content is stable for one year at ambient temperature (mean 22.3°C) in HDPE.
Corrosion characteristics	The product is not corrosive to its HDPE packaging material.	
Explosibility	Not explosive when subjected to flame or shock.	Not explosive

### 1.3 Directions for Use

Sivanto 200 SL controls aphids, leafhoppers, whiteflies, Colorado potato beetle, scale insects, and blueberry maggot and suppresses pear psylla at 500-750 or 750-1000 mL product/ha. It is applied by ground application to the foliage of Crop Group (CG) 4-13 (Leafy Vegetables), CG 5-13 (Brassica Head and Stem Vegetables), CG 6 (Legume Vegetables), CG 8-09 (Fruiting Vegetables), CG 9 (Cucurbits), CG 11-09 (Pome Fruit) and CG 14-11 (Tree Nuts), Crop Subgroups 1B (Root Vegetables, except sugarbeet), 1C (Tuberous and Corm Vegetables), 13-07B (Berry and Small Fruit, except highbush cranberry), 13-07F (Berry and Small Fruit – vine including grapes), 13-07G (Berry and Small Fruit – low growing berries including strawberries, except lowbush blueberry and lowbush cranberry) and 22B (Leaf Petiole Vegetables), and corn (field, sweet, pop and seed), alfalfa, peanuts and hops. Sivanto 200 SL is applied by aerial application to the foliage of Crop Group 6, and Crop Subgroups 1B and 1C. Soil application may be made to Crop Groups 8-09 and 9 at 750-1000 mL product/10,000 plants and to Crop Subgroup 13-07F at 1500-2000 mL product/ha. A maximum of 400 g flupyradifurone may be applied per hectare per year. See Appendix I, Table 32 for details.



BYI 02960 480 FS, a seed treatment for soybean, controls soybean aphids and bean leaf beetle adults at 13.3-20 mL/140,000 soybean seeds. BYI 02960 480 FS may be tank mixed with EverGol Energy, EverGol Xtend, Allegiance FL, Trilex AL Concentrate and Trialex FS as per instructions on the product labels. A maximum of 400 g flupyradifurone may be applied per hectare per year.

#### **1.4 Mode of Action**

Flupyradifurone interferes with the function of insect nerves causing paralysis and death. Flupyradifurone is active by ingestion and contact, but is more potent via ingestion. This active ingredient is systemic when applied as a soil treatment and has translaminar activity when applied as a foliar treatment.

### **2.0 Methods of Analysis**

#### **2.1 Methods for Analysis of the Active Ingredient**

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

#### **2.2 Method for Formulation Analysis**

The methods provided for the analysis of the active ingredient in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

#### **2.3 Methods for Residue Analysis**

Methods for residue analysis are summarized in Appendix I, Table 1. High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media (soil and sediments, water).

Enforcement Method, Method RV-001-P10-02/03 (a.k.a 01304), a high pressure liquid chromatography with tandem mass spectrometry (HPLC-MS/MS), developed for the analysis of flupyradifurone and its metabolites (difluoroacetic acid (DFA) and difluoroethyl-amino-furanone (DFEAF)) in plants and processed commodities, was validated on a varied group of representative crop matrices. Residues are extracted from plant matrices twice using a mixture of acetonitrile/water (4:1, v/v) with formic acid (2.2 mL/L). Aliquots of the extracts were purified through a C-18 solid-phase extraction column. After dilution, an aliquot was analysed by reverse-phase HPLC with electrospray MS/MS. Residues were quantified against internal standards. The limit of quantitation (LOQ) for flupyradifurone, defined as the lowest validated fortification level, was 0.01 mg/kg in all matrices tested, except hop cones, in which it was 0.05 mg/kg. For DFA, the LOQ was 0.02 mg/kg in wet matrices, and 0.05 mg/kg in dry matrices. The



method was also tested for and proven to be capable of determining the metabolite DFEAF in all sample materials, with an LOQ of 0.01 mg/kg; however, DFEAF and DFA are not part of the residue definition for enforcement. Generally, acceptable recoveries (70-120%) of flupyradifurone and analytes were obtained in plant and processed commodities at spiking levels that bracket the expected residues.

The proposed enforcement method was successfully validated by independent laboratory using tomatoes, oranges, lentils, and soybeans. Adequate extraction efficiencies were demonstrated in plant matrices using radiolabelled samples from plant metabolism studies and confined rotational crops such as tomatoes, cottonseeds, potato tubers, and wheat straw.

The HPLC-MS/MS method, RV-004-A11-05, for the determination of flupyradifurone, DFA, BYI 02960-acetyl-AMCP, and BYI 02960-OH in livestock tissues, milk and eggs, involved extraction using a mixture of acetonitrile/water (4:1, v/v) with formic acid (2.2 mL/L). Aliquots of the extracts were purified through a C-18 solid-phase extraction column. After dilution, an aliquot was analysed by reverse-phase HPLC with electrospray MS/MS. Residues were quantified against internal standards. The LOQ is 0.01 ppm for all analytes in all matrices, with the exception of DFA in bovine tissues (0.02 mg/kg). Acceptable recoveries (70-120%) of flupyradifurone and analytes were obtained in animal matrices, including eggs, and milk, at spiking levels that bracket the expected residues. The method was successfully validated by independent laboratory using bovine milk, and liver. Adequate extraction efficiencies were demonstrated in animal matrices using radiolabelled samples from the livestock metabolism studies such as eggs, poultry tissues (fat, liver, and muscle), and bovine milk and kidney.

### **3.0 Impact on Human and Animal Health**

#### **3.1 Toxicology Summary**

Flupyradifurone, also known as BYI 02960, is a member of the butenolide class of chemicals and acts by binding to the nicotinic acetylcholine receptor. Normally, the neurotransmitter acetylcholine, which is released at neuronal and neuromuscular junctions in response to membrane depolarization, binds to the nicotinic acetylcholine receptor causing ion channels to open, leading to changes in ion flux and perpetuating the nerve impulse. When acetylcholine is subsequently destroyed by the enzyme acetylcholinesterase, the membrane returns to its normal resting state. However, binding of nicotinic acetylcholine agonists to the nicotinic acetylcholine receptor leads to prolonged activation of the receptor, causing desensitization and blocking of the receptor. The result of such agonistic activity is excitation of the nervous system.

A detailed review of the toxicological database for flupyradifurone was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. With the exception of the dermal sensitization study conducted with the active ingredient flupyradifurone, the studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to flupyradifurone.

In acute toxicity testing in rats, flupyradifurone was demonstrated to be slightly toxic via the oral route and of low toxicity via the dermal and inhalation routes. Flupyradifurone was shown to be non-irritating to the skin and minimally irritating to the eyes of rabbits. A modified local lymph node assay (LLNA) conducted in mice to assess the dermal sensitization potential of flupyradifurone yielded negative results (PMRA 2239544). The protocol used in this study differed from currently recognized international test guidelines. The submitted modified LLNA was a non-radioactive modification of the traditional LLNA as described in OECD Test Guideline 429 Performance Standards. Data were not provided to demonstrate that this protocol met the requirements for intra- and inter laboratory reproducibility for the modified LLNA (as per OECD Test Guideline 429 Performance Standards); as such, the accuracy and reproducibility of this modified LLNA for regulatory purposes remains to be established. It is further noted that test concentrations were not maximized in the submitted modified LLNA study. Thus, it has not been established that flupyradifurone is not a skin sensitizer from the submitted data.

In acute toxicity testing in rats, the end-use product, BYI 02960 480 FS, was demonstrated to be slightly toxic via the oral route and of low toxicity via the dermal and inhalation routes. In rabbits, it was shown to be minimally irritating to the skin and non-irritating to the eyes. BYI 02960 480 FS is not a dermal sensitizer based on results from an acceptable LLNA in mice.

The end-use product, Sivanto 200 SL, was demonstrated to be of low acute toxicity via the oral, dermal and inhalation routes in rats, and non-irritating to the skin and minimally irritating to the eyes of rabbits. Sivanto 200 SL is a dermal sensitizer based on results from an acceptable LLNA in mice.

The toxicokinetics of flupyradifurone following a single oral low dose was investigated in rats using three different radiolabel positions. The active ingredient was labeled with  $^{14}\text{C}$  either in the pyridinylmethylene bridge, the 4-position of the furanone ring, or the 1-position of the ethyl side chain. Absorption was high (>80% of the administered dose) and rapid, with the maximum plasma concentration reached within one hour post-dosing in both male and female rats for all three radiolabel positions. Administration of a high dose of flupyradifurone, which was limited to the pyridinylmethylene bridge radiolabel, also resulted in high (>76% of the administered dose) and rapid absorption, with the maximum plasma concentration reached within four hours of dosing.

Following single oral low and high doses, elimination of radioactivity was nearly complete within 72 hours of dosing, and occurred primarily via the urine, which accounted for over 75% of the administered radioactivity. The radioactivity detected in feces accounted for less than 26% of the administered dose, while elimination through expired air was negligible, for both low and high dosing regimens.

Flupyradifurone was rapidly distributed to tissues following oral administration; however, within three to seven days of dosing the levels of radioactivity remaining in tissues were minimal for both low and high doses. Quantitative whole body autoradiography studies conducted with low doses of the pyridinylmethyl or the furanone radiolabel of flupyradifurone showed that maximum tissue levels were reached one hour following dose administration, with the highest residue levels detected in the liver, kidney and hormonal/secretory glands (thyroid, adrenal, Harderian, salivary glands) for both radiolabels, and in the brown fat, myocardium and olfactory bulb for the furanone-label. Tissue levels declined rapidly thereafter.

The parent compound was the predominant component detected in urine (up to 74% of the administered dose) for all three radiolabels following administration of low and high doses. The parent compound was also the predominant component in organs and tissues (composing greater than 72% of the total radioactive residues) following administration of the furanone radiolabel, while the metabolite difluoroacetic acid made up a significant portion (>50%) of the total radioactivity detected in organs and tissues following administration of the ethyl radiolabel.

The principal metabolic reactions of flupyradifurone in rats involve 1) hydroxylation followed by conjugation with glucuronic acid or sulfate, 2) cleavage of the difluoroethyl group forming BYI 02960-des-difluoroethyl and difluoroacetic acid, and 3) cleavage at the pyridinylmethyl bridge forming 6-chloronicotinic acid, with further conjugation with glycine to BYI 02960-hippuric acid and BYI 02960-difluoroethyl-amino-furanone. While the metabolic profiles were similar between male and female rats, male rats demonstrated a higher rate of metabolite formation than female rats.

Although there was no repeated-dosing regimen included in the toxicokinetics studies conducted with flupyradifurone, plasma concentrations of flupyradifurone were determined in several repeated-dose dietary studies. In the 90-day dietary study in mice, the concentration of flupyradifurone in plasma samples collected at study termination were determined to increase linearly with dose, and were slightly higher in male mice than in female mice. A different trend was observed in plasma samples collected from rats at the end of the 90-day dietary study. Slightly higher concentrations of flupyradifurone were noted in females when compared to males, and concentrations increased linearly at lower doses only; a sublinear increase in plasma concentration was observed in both sexes at the high dose. In the one-year dog study, plasma concentrations of flupyradifurone were determined in dogs from only the control and mid-dose groups only after 20 weeks of dosing at 1, 3, and 8 hours after withdrawal of food. Plasma concentrations in mid-dose dogs peaked at 3 hours after removal of food and were slightly higher in males than in females. In the long-term rat and mouse studies, plasma samples were collected for the determination of flupyradifurone levels at interim sacrifice (after one year of dosing in both studies) and at study termination (after 18-months in mice and two years in rats). The levels of parent compound increased linearly with dose in both sexes of mice and in female rats, but in a sublinear fashion for male rats. In mice, flupyradifurone levels were slightly higher in males than in females, whereas in rats, levels were generally higher in females than in males. In both studies, the levels at interim sacrifice were not significantly different from those measured at study termination.



No adverse systemic or dermal effects were observed in a 28-day dermal toxicity study in rats up to the highest dose. A repeated-exposure inhalation toxicity study was not conducted with flupyradifurone. A waiver for this data requirement for the petitioned uses was accepted on the basis of the low volatility of flupyradifurone (vapor pressure of  $9.1 \times 10^{-10}$  to  $2.6 \times 10^{-8}$  kPa at 20°C to 50°C) and the margins of exposure calculated when using a toxicological endpoint from an oral toxicity study. A repeated exposure inhalation study may be required for future use expansion of flupyradifurone, however.

In short-term oral studies conducted in the mouse, dog, and rat, flupyradifurone was administered via the diet for 28 and 90 days. Rats were also administered flupyradifurone in corn oil via gavage for 28 days. Reductions in body weight were observed in all species. The liver was also a target of toxicity common to all three species. In mice and rats, increased liver weights and incidences of hepatocellular hypertrophy were observed, along with associated changes in clinical chemistry parameters, such as protein, cholesterol, bilirubin and triglyceride levels in plasma. Treatment-related hepatic effects that were limited to the rat included lobulation and enlargement of the liver, while in dogs only, an accumulation of brown pigment in Kupffer cells was observed. Slight elevations in liver enzymes were noted in all three species. The effects on the liver that were noted in rats after 90 days of dosing were no longer apparent after a 28-day recovery period.

Additional target organs of toxicity noted in the short-term studies included the kidney in the mouse, the thyroid gland in the rat and dog, and skeletal muscle in the dog. Renal effects in the mouse included decreased kidney weight and loss of normal cortical epithelial vacuolation in males after 90 days of dosing. In the rat, increased thyroid weight and thyroid follicular cell hypertrophy were observed in both sexes but occurred in males at lower doses than in females. Elevations in thyroid stimulating hormone and reductions in thyroxine, which were measured in male rats only, were observed after 28 days of dietary dosing. The thyroid gland effects noted in rats were demonstrated to be reversible after a 28-day recovery period. An enlarged thyroid gland, increased thyroid weight, and thyroid follicular dilatation were observed in the dog but only at high doses following 28 days of dietary administration. Atrophy and degeneration of skeletal muscle fiber were observed in both sexes at the LOAEL in the 90-day dietary study in the dog. At higher doses, clinical manifestations of muscle fiber degeneration were apparent in two of four dogs in the form of unsteadiness and stiffness of the back legs and lower back. In the one-year dietary study in dogs, histopathological evidence of skeletal myofiber degeneration was again noted in both sexes. The degeneration was associated with atrophy, necrosis and/or the presence of inflammatory cells around the affected myofiber. The clinical manifestations of skeletal muscle fiber degeneration that were observed in the 90-day study were not seen in the one-year study because a dose level comparable to the dose that elicited clinical signs of toxicity in the 90-day study was not used in the one-year study.

In rodents, a similar spectrum of effects as those seen in the short-term toxicity studies was noted with longer-term dosing. Target organs of toxicity included the liver and kidney in the 18-month dietary study in the mouse, and the liver and thyroid gland in the two-year dietary study in the rat. Liver toxicity was manifested as increased weight, hepatocellular hypertrophy, alterations in the normal vacuolation of hepatocytes, brown pigmentation of Kupffer cells, and interstitial mononuclear cell infiltrate. Renal effects in the mouse, which were only observed in males, included atrophy of the kidney, reduced kidney weight, and altered mineralization and vacuolation of cortical epithelial cells. In the rat, colloid alteration and thyroid follicular cell hypertrophy were observed in both sexes, while brown pigmentation of the thyroid follicular cells was noted in females only.

Additional effects noted only in female rats after chronic dosing in the two-year dietary study included lens opacity and lung tissue lesions (white foci, alveolar foamy macrophages, chronic interstitial/perivascular inflammation). Overall, there were indications supporting a slight increase in toxicity with prolonged duration of dosing with flupyradifurone, based on these unique findings, as well as slight reductions in effect levels in rats and mice following long-term dosing when compared to those following short-term exposure.

Slight alterations in red blood cell parameters were noted in selected studies conducted with flupyradifurone. These included slight reductions in red blood cell counts, hematocrit and hemoglobin at the highest dose tested in the 90-day dietary study in dogs and slight decreases in various parameters (hemoglobin, hematocrit, mean cell volume, and mean corpuscular hemoglobin) in female rats in the two-year dietary study. These were the only hematology changes observed in the database and they occurred in the presence of other organ system effects.

There was no evidence of genotoxicity when flupyradifurone was tested in a battery of in vivo and in vitro genotoxicity studies. Additionally, there was no evidence of oncogenicity in long-term dietary studies conducted in the rat and mouse.

In a 28-day dietary immunotoxicity study conducted in rats, no evidence of dysregulation of the immunological system was apparent. The only perturbation to the immune system in the toxicological database was a decrease in spleen weight in the 28-day oral gavage study in the rat, which was not accompanied by any pathological correlates and occurred at doses that elicited liver and thyroid effects. Overall, there was no evidence to indicate that flupyradifurone selectively targets the immune system.

Consistent with effects seen in other repeat-dosing toxicity studies, effects on the liver and thyroid gland were apparent in parental male animals in the two-generation dietary reproductive toxicity study in rats. The liver was affected in the first parental generation only, in the form of increased weight and hepatocellular hypertrophy. Thyroid weights were elevated in both parental generations; the thyroid gland was not assessed histologically in this study. Body weight reductions in parental females of the first generation carried over into the second generation of parental animals. In offspring of both generations, body weights were decreased during the post-natal period at the same dose level that resulted in the parental effects noted above. At the next lower dose level, which did not elicit adverse effects in parental animals, the body weights of F2



offspring were slightly reduced toward the end of the post-natal period only. Effects on the reproductive system were noted at the highest dose. In males, these effects included decreased epididymal and testicular sperm counts in the P and/or F<sub>1</sub> generation. Decreases in the number of estrous cycles and implantation sites were observed in F<sub>1</sub> females, resulting in a decrease in the number of pups born and reduced mean litter size of F<sub>2</sub> pups. Of note is that the only other effect on reproductive related tissues in the toxicological database was an increase in prostate weight in dogs at the highest dose in the 90-day dietary study.

Following in utero exposure where maternal rats received flupyradifurone via gavage, developmental effects were noted in fetuses at the highest dose tested and included incomplete ossification of the parietal and hyoid centra. Maternal toxicity was evident at this dose in the form of body weight loss, reduced food consumption and salivation. For assessing the potential for developmental toxicity in rabbits, results from both the oral gavage dose range-finding study and the main study were considered together. In the dose range-finding study, a serious developmental effect was observed in the presence of maternal toxicity. Maternal effects included body weight loss and reduced fecal output. At the same dose level, an increased number of dead fetuses and a reduction in fetal body weight were apparent. No adverse effects were apparent up to the highest dose in the main study. Based on the combined results from these two studies, the maternal and developmental LOAEL were established at the highest dose in the dose range-finding study.

In acute neurotoxicity testing, several treatment-related effects were observed on the day of dosing, some of which were consistent with overstimulation of nicotinic acetylcholine receptors. These effects included piloerection, pupil dilation, tremors, impaired gait, altered reflexes, and decreased motor activity. There was no effect of treatment on various neurotoxicity parameters assessed in rats at the end of the 90-day dietary study or in the 90-day dietary neurotoxicity study. In a dietary developmental neurotoxicity (DNT) study conducted in rats, treatment-related increases in motor and locomotor activity were observed in male offspring at post-natal day (PND) 13 and in auditory startle response in female offspring on PND 60. This dose level also resulted in body weight reductions in maternal animals during gestation and in their offspring during the lactation phase. Overall, the effects observed in the DNT study were considered marginal, resulting in low overall concern for developmental neurotoxicity following exposure to flupyradifurone.

Additional toxicity studies were conducted on four metabolites of flupyradifurone, including (6-chloro-3-pyridyl) methanol (found in plants), 6-chloronicotinic acid (found in the rat, crops, soil and livestock), difluoroacetic acid (found in the rat, crops, soil and livestock), and BYI 02960-difluoroethyl-amino-furanone (found in the rat and crops). All four metabolites were evaluated for acute oral toxicity in rats, as well as for genotoxic potential. Two of these metabolites, (6-chloro-3-pyridyl) methanol and difluoroacetic acid, were demonstrated to be of slight toxicity, while the metabolites 6-chloronicotinic acid and BYI 02960-difluoroethyl-amino-furanone were determined to be of low acute toxicity via the oral route. An increase in the frequency of chromosomal aberrations in the absence of metabolic activation was observed in Chinese hamster V79 lung cells exposed in vitro to BYI 02960-difluoroethyl-amino-furanone; however, this metabolite produced negative results in two other in vitro genotoxicity studies and in two in vivo genotoxicity studies. In vitro genotoxicity studies conducted on the other metabolites were all negative. Overall, the metabolites were not considered to have genotoxic potential.

Short-term dietary studies were also conducted with three of the metabolites mentioned above. In a 28-day dietary study conducted in rats with the metabolite BYI 02960-difluoroethyl-amino-furanone, no adverse effects were noted up to the highest dose tested, which exceeded the dose levels used in studies conducted with the parent compound. The metabolite (6-chloro-3-pyridyl) methanol was administered to rats for 90 days via the diet. Treatment-related findings included kidney effects (eosinophilic intranuclear inclusions in proximal tubular epithelium) as well as body weight reductions, which were observed at higher dose levels than those eliciting similar effects in repeated-dose dietary studies conducted with the parent compound. Testing with the metabolite difluoroacetic acid, which was also administered to rats via the diet for 90 days, resulted in increases in urinary volume and urinary ketone levels and a slight increase in the incidence of erosion/necrosis of the glandular stomach. These effects were not seen in any studies conducted with the parent compound. When comparing the doses and effect levels for the parent compound with those for the metabolite difluoroacetic acid, it could not be definitively concluded that difluoroacetic acid was less toxic than the parent. No repeated-dose dietary study was conducted with 6-chloronicotinic acid.

Results of the toxicology studies conducted on laboratory animals with flupyradifurone, its metabolites, and its associated end-use products are summarized in Appendix I, Tables 2, 3 and 4. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 5.

### **Incident Reports**

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Incidents were searched and reviewed for the active ingredient flupyradifurone. Since flupyradifurone is a new active ingredient pending registration for use in Canada, there have been no incident reports submitted to the PMRA involving flupyradifurone.

### 3.1.1 Pest Control Products Act Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the standard complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats. In addition, a DNT study in rats is available.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the rat developmental toxicity or DNT studies. In the developmental toxicity study, an increased incidence of incomplete ossification of the parietal and hyoid centra was observed in the presence of maternal toxicity, manifested as body weight loss, decreased food consumption, and salivation. Offspring from the DNT study exhibited delayed growth during the post-natal period, as well as mild functional effects in the form of increased motor and locomotor activity in males on PND 13 and increased auditory startle response in females on PND 60. At the same dose level, reductions in body weight were observed in maternal animals. The level of concern for the behavioural effects noted in the DNT study was low, considering that the effects were generally marginal and were observed in the presence of maternal toxicity.

In the rat two-generation reproductive toxicity study, decreased offspring body weight was observed toward the end of the lactation period at a dose that did not elicit parental toxicity. However, there is a low concern for sensitivity of the young observed in this study, considering the nature, degree and timing of the effect, which occurred from lactation day 14 onward when there is the potential for consumption of the test diet by the offspring in addition to exposure that may be occurring via lactation. On the basis of the combined results of the dose range-finding and main rabbit developmental toxicity studies, a serious endpoint (fetal death) was observed at a dose level that resulted in body weight reductions in maternal animals.

Overall, the database is adequate for determining the sensitivity of the young and effects on the young are well-characterized. The *Pest Control Products Act* factor was reduced to 3-fold for exposure scenarios using the toxicological endpoint from the rabbit developmental toxicity studies, in which a serious endpoint was observed in the presence of maternal toxicity. For all other exposure scenarios, the *Pest Control Products Act* factor was reduced to 1-fold.



### 3.2 Acute Reference Dose (ARfD)

#### Females 13 to 49 Years of Age

For females 13 to 49 years of age, the most appropriate study endpoint for assessing risk following acute dietary exposure to flupyradifurone was from the combined developmental toxicity studies in the rabbit. Based on the combined results from the dose range-finding study and the main developmental toxicity study, the developmental NOAEL was established at 40 mg/kg bw/day, based on increased fetal death at the LOAEL of 80 mg/kg bw/day. The critical endpoint of fetal death noted in this study may occur following a single in utero exposure; therefore, these effects are relevant to the selection of this ARfD for this sub-population. Other effects noted in these combined studies included reduced maternal and fetal body weights at 80 mg/kg bw/day.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 3-fold for exposure scenarios using the toxicological endpoint from the rabbit developmental toxicity studies. The composite assessment factor (CAF) is 300.

The ARfD (for females 13 to 49 years of age) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{40 \text{ mg/kg bw}}{300} = 0.13 \text{ mg/kg bw}$$

#### General Population

For the general population, the most appropriate endpoint for assessing risk following acute dietary exposure to flupyradifurone was from the acute neurotoxicity study in the rat. In that study, a NOAEL of 35 mg/kg bw was determined, based on clinical signs of toxicity (piloerection and pupil dilation) noted on the day of dosing. The toxicological effects noted in animals in this study occurred following a single exposure; therefore, these effects are relevant to the selection of the ARfD.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The CAF is 100.

The ARfD (general population) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{35 \text{ mg/kg bw}}{100} = 0.35 \text{ mg/kg bw}$$

### 3.3 Acceptable Daily Intake (ADI)

To estimate risk from chronic dietary exposure to flupyradifurone, the results from both the one-year dietary study in the dog and the two-generation reproductive toxicity study in the rat were considered as co-critical studies. The effect levels established in these studies were similar, and both studies revealed critical endpoints of concern. In the one-year dog study, the NOAEL of 7.8 mg/kg bw/day was established for both sexes based on an increased incidence of skeletal muscle myofiber degeneration and reduced body weight gain that were observed at the LOAEL of 28 mg/kg bw/day. In the two-generation reproductive toxicity study in the rat, the NOAEL of 7.8 mg/kg bw/day was established in offspring, based on effects at the LOAEL of 39 mg/kg bw/day that included reduced body weights in the F2 generation occurring towards the end of the lactation period.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{7.8 \text{ mg/kg bw/day}}{100} = 0.08 \text{ mg/kg bw/day}$$

This ADI provides a margin of 500 to the NOAEL for fetal deaths observed in the combined rabbit developmental toxicity studies.

### Cancer Assessment

As there was no evidence of carcinogenicity, a cancer risk assessment was not necessary.

### 3.4 Occupational Risk Assessment

#### 3.4.1 Toxicological Endpoints for Occupational Exposure Assessments

Occupational exposure to flupyradifurone is characterized as short- to intermediate-term duration and is predominantly by the dermal and inhalation routes for mixers, loaders, applicators, workers handling treated seed and farmers planting treated seed and by the dermal route for workers re-entering treated fields.

For assessing risk from short-, intermediate- and long-term occupational exposure via the dermal and inhalation routes, the results from both the one-year dietary study in the dog and the two-generation reproductive toxicity study in the rat were considered as co-critical studies. No repeated exposure inhalation toxicity study was available, and the available 28-day dermal toxicity study was not considered appropriate for endpoint selection as it was conducted in the rat and not the dog, which was demonstrated to be the most sensitive species for the critical effect of skeletal myofiber degeneration.

The effect levels established in the one-year dog study and the two-generation reproductive toxicity study were similar, and both studies revealed critical endpoints of concern. In the one-year dog study, the NOAEL of 7.8 mg/kg bw/day was established for both sexes based on an increased incidence of skeletal muscle myofiber degeneration and reduced body weight gain that were observed at the LOAEL of 28 mg/kg bw/day. Similar effects were also noted in dogs at a comparable dose level after 90 days of dosing.

In the two-generation reproductive toxicity study in the rat, the NOAEL of 7.8 mg/kg bw/day was established in offspring, based on effects at the LOAEL of 39 mg/kg bw/day that included reduced body weights in the F2 generation occurring towards the end of the lactation period. Although the effect on offspring body weight may have reflected both dietary and lactational exposure, the relevance of this endpoint to the occupational exposure scenarios cannot be excluded as the effect was seen as early as PND 14.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The target margin of exposure (MOE) is 100 for all scenarios. The selection of this endpoint and MOE is considered protective of sensitive sub-populations, such as women of reproductive age, pregnant women, and unborn children.

#### **3.4.1.1 Dermal Absorption**

A triple pack of rat in vitro and in vivo and human in vitro studies using radiolabelled flupyradifurone were conducted using the 200 SL formulation at nominal dosing levels of 200 g a.i./L, 0.625 g a.i./L and 0.1 g a.i./L. The formulation concentrations and application rates were designed to mimic potential field-use exposures.

In the in vivo study flupyradifurone was administered for 8 hours to Wistar rats over four sacrifice timepoints of 8, 24, 72, or 168 hours. The directly absorbed dose was considered to be the dose recovered in the urine, faeces, cage washes, cardiac blood and carcass. Radiolabel in tape strips and skin, including surrounding skin, untreated skin, and skin at dose site were regarded as being potentially absorbable. The terminal skin wash was not included in the potentially absorbable dose, even though absorption and excretion continued until the 168 hour time period, because it was considered relatively conservative. The majority of the dose was recovered in the skin wash after the 8 hour exposure period and, of the absorbed dose, the highest recoveries were recorded in the tape strips (1-20). The main route of excretion was urine. At 168 hours, the dermal absorption range at the high dose was 9.44 to 30.5% with an average of 19.6% ( $\pm$  8.8), at the intermediate dose was 4.66 to 12.0% with an average of 7.16% ( $\pm$  3.4) and at the low dose was 20.5 to 27.2% with an average of 24.3% ( $\pm$  3.4). No major deficiencies were noted in the study; however, it was not quantitatively used as the range of doses tested did not comply with EPA guideline OPPTS 870 7600.

In the in vitro studies, dermal absorption of flupyradifurone was tested using rat (dorsal) and human (abdominal) skin mounted in a glass flow-through diffusion cell system with an exposure area of 1 cm<sup>2</sup>. The exposure duration was 8 hours after which receptor fluid samples were collected hourly for the 24 hour duration of the study. The directly absorbed dose included the



dose recovered in the receptor fluid and in the receptor chamber. The potentially absorbed dose included the dose recovered in the treated skin, the tape strips and the surrounding skin. For all doses, the highest recoveries were recorded in the skin wash and the highest recoveries in the absorbed fraction were recorded in the skin at the test site (including tape strips). The range of total absorbed dose for the rat skin samples at the high dose was 0.068 to 0.751% with an average of 0.291% ( $\pm 0.16$ ), at the intermediate dose was 1.68 to 17.7% with an average of 7.81% ( $\pm 6.9$ ), and at the low dose was 10.3 to 18.8% with an average of 12.5% ( $\pm 4.3$ ). The total absorbed dose for the human skin samples at the high dose was 0.0355 to 0.863% with an average of 0.349% ( $\pm 0.34$ ), at the intermediate dose was 0.881 to 3.65% with an average of 2.51% ( $\pm 1.3$ ), and at the low dose was 1.27 to 9.32% with an average of 5.75% ( $\pm 3.4$ ). Comparing the average dose/duration values, the human/rat in vitro dermal penetration values were 0.349%/0.291%, 2.51%/7.81% and 5.75%/12.5% for the 200 g/L, and 0.625 g/L, and 0.1 g/L dose levels, respectively. No major deficiencies were noted in the in vitro studies; however the number of skin samples per dose level and duration were not in accordance with PMRA guidelines (2012). The low number of skin sample replicates may have contributed to the variability (standard deviation greater than 25%) in in vitro results. Hence, the dermal absorption value used for risk assessment purposes was on the high end of the dermal absorption range.

The studies were similar in dose levels, duration of exposure, testing conditions and followed the OECD (2011) guidelines, which justified using the NAFTA triple pack approach. While no major deficiencies were found in either study, the high variability in the data required some correction in the final dermal absorption value used for risk assessment purposes. When comparing the mean dermal absorption values at 24 hours for each dose, the in vitro/in vivo rat ratio approximated 1 at the intermediate and low doses. OECD guidelines suggest accounting for highly variable data by choosing a dermal absorption value based on the mean plus one standard deviation. Based on this, a dermal absorption value of 9.0% was chosen from the human in vitro study at the low dose following a 24-hour duration. This value is the mean (5.75%) plus one standard deviation (3.4%). The 9% dermal absorption value is an acceptable estimate of dermal absorption to postapplication workers that re-enter fields treated with diluted end-use products.

Based on the absorption characteristics of flupyradifurone, choosing a separate dermal absorption value for workers handling the concentrated flupyradifurone end-use products is appropriate. This is based on the fact that the in vivo dermal absorption values at the higher dose levels were higher than those at the intermediate dose levels which were slightly lower than those at the lower dose level. The typical trend in dermal absorption studies is that the highest dose has the lowest dermal absorption value. Also, for the in vitro study at the high dose level, absorption of the test substance was greater through human skin than rat skin which is atypical. Finally, while the high dose level of 200 g/L (2 mg/cm<sup>2</sup>) represents the neat product which chemical handlers will be exposed to, this high dose level greatly exceeds the highest dose recommended in the USEPA guidelines (0.1 mg/cm<sup>2</sup>). Dermal absorption characteristics are expected to be very different depending on the level of dilution of the test substance. Due to these factors, the dermal absorption value of 9% was not considered appropriate for mixers, loaders, and applicators. The NAFTA Triple Pack approach cannot be used to approximate a human in vivo dermal absorption value as the rat in vitro/in vivo ratio did not approximate 1. As such, a dermal absorption value of 28% was adopted from the rat in vivo study at the 168 hour

monitoring period from the low dose group (0.1 g a.i./L). This value is the mean (19.6%) plus one standard deviation (8.8%) at that dose and duration based on the high variability in the data.

### **3.4.2 Occupational Exposure and Risk**

#### **3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment**

##### *BYI 02960 480 FS*

Soybeans can be treated with BYI 02960 480 FS in commercial seed treatment facilities or by commercial mobile treaters, and planted using conventional seeding equipment. Exposure to workers mixing, loading and applying flupyradifurone is expected to be short- to intermediate-term in duration and to occur primarily by the dermal and inhalation routes.

Chemical-specific data for assessing treater, bagger and cleaner exposures during pesticide handling activities were not submitted. For assessing exposure during seed treatment in commercial operations, a surrogate passive dosimetry study measuring the exposure of mixers/loaders/calibrators (treaters), baggers/sewers/stackers and cleaners at commercial facilities treating corn and canola with a variety of active ingredients was used (Krolski, 2010). The study determined the dermal and inhalation exposure of workers performing commercial seed (canola and corn) treatment activities using closed transfer systems. A total of twenty four male workers were monitored during the study. Dermal exposure was estimated by measuring residues on or in the inner whole body dosimeters, face/neck wipes, and hand washes. Inhalation exposure was estimated by measuring residues in personal air samplers fitted with an OVS tube. Three different job activities were monitored at the sites: 1) treatment of seed, including mixing, loading and operation of the seed treatment equipment; 2) packaging of treated seeds, including bagging, sewing, stacking and forklift operations; and 3) cleaning of seed treatment and seed handling equipment. The dermal and inhalation exposure values are expressed as  $\mu\text{g/kg ai}$  handled for treaters and baggers/sewers/stackers. The dermal exposure to equipment cleanout operators is provided in  $\mu\text{g/g ai/100 kg seed}$ , hence it is not possible to determine the amount of active ingredient handled per day for cleaners. Therefore, exposure to these workers was normalized by the mean application rate used over the treatment period.

A seed treatment dust-off study was conducted to compare the dust-off potential of soybean seeds treated with BYI 02960 480 FS with the dust-off potential of the seeds treated with other formulations that support the use of the surrogate passive dosimetry study data. Seed treatment dust-off experiments were conducted using untreated and treated soybeans. The study report concluded that dust-off potential of BYI 02960 480 FS treated soybeans are generally equal to or lower than that from surrogate test material-treated crops. Therefore, the surrogate seed treating and planting studies should not underestimate exposure while treating or planting flupyradifurone treated soybeans.

Exposure estimates were derived for mixers/loaders/applicators applying flupyradifurone to treat soybeans using closed transfer systems including closed mixing, loading, calibrating and closed treatment equipment. The exposure estimates are based on mixers/loaders/applicators wearing coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks. Other workers in commercial seed treatment facilities, such as baggers and cleaners, are expected to be exposed from the dermal and inhalation routes and for a short- to intermediate-term duration. The exposure estimates are based on baggers and cleaners wearing long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks.

Commercial seed treating capacities were derived from the PMRA commercial default throughput values. The default amount of soybean seed (63 000) treated per day was used to estimate exposure on a typical 8 hour work day.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value of 28% for treaters/applicators and 9% for baggers/sewers/stacker and cleaners. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposures were normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological end points (no observed adverse effects levels) to obtain the margin of exposure (MOE); the target MOE is 100. Inhalation and dermal risks to workers were not of concern (MOEs were above the target MOE; Appendix I, Table 6).

#### *Sivanto 200 SL*

Individuals have potential to be exposed to Sivanto 200 SL during mixing, loading and application. Exposure is expected to be short- to intermediate-term in duration and to occur primarily by the dermal and inhalation routes.

Dermal and inhalation exposure estimates were derived for mixers/loaders/applicators applying flupyradifurone to a variety of crops using open cab groundbooms, backpacks, hand held (manually- and mechanically-pressurized) sprayers, soil injection, and chemigation using unit exposure values from the Pesticide Handler Exposure Database (PHED) v3.1. and the Agricultural Handlers Exposure Task Force (AHETF). All exposure estimates are based on mixers/loaders/applicators using equipment and wearing PPE that is in keeping with label instructions.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 28% dermal absorption. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using an 80 kg adult body weight.

Exposure estimates were compared to the toxicological end points (no observed adverse effects levels) to obtain the margin of exposure (MOE); the target combined MOE is 100.



Dermal and inhalation risks to workers mixing, loading and applying flupyradifurone were not of concern (MOEs were above the target MOE; Appendix I, Table 7).

#### **3.4.2.2 Exposure and Risk Assessment for Planters of Treated Seed**

Individuals have potential for exposure to flupyradifurone while planting treated seed through dermal and inhalation routes. Exposure is expected to be short-term in duration. Chemical specific data for assessing human exposure during planting of treated seed were not submitted. As such, surrogate exposure data were used to estimate risk to workers planting treated seed.

For assessing exposure during planting of flupyradifurone treated seeds, a previously reviewed surrogate passive dosimetry study that measured the exposure of workers loading and planting treated seed was used (Zietz, 2008). Sixteen workers were monitored while opening bags, loading seed into a hopper and planting seeds (closed-cab), cleanup and repair while wearing a single layer and gloves. Dermal exposure for each worker was measured using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. Inhalation exposure for each worker was measured by means of a personal air sampling pump. Exposure values were normalized for the amount of active ingredient handled per day. The arithmetic mean was used for all activities as replicate numbers and field recoveries were sufficient.

The PMRA default seeding rate of 90 kg/ha and 100 hectares planted per day were used.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 9% dermal absorption. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using an 80 kg adult body weight.

Exposure estimates were compared to the toxicological end points (no observed adverse effects levels) to obtain the MOE; the target combined MOE is 100. Dermal and inhalation risks to workers were not of concern (MOEs were above the target MOE; Appendix I, Table 8). As the surrogate passive dosimetry study assessed exposure using closed cab tractors, this restriction must be on the label for BYI 02960 480 FS.

#### **3.4.2.3 Exposure and Risk Assessment for Workers Entering Treated Areas**

There is potential for exposure to workers re-entering areas after foliar application of Sivanto 200 SL to perform activities such as hand harvesting, hand girdling, detasseling, thinning, and setting irrigation lines by hand. Given the nature of activities performed, dermal contact with treated crops should be short- to intermediate-term in duration. Inhalation exposure is not expected to be of concern given the non-volatile nature of flupyradifurone and restricted entry interval (REI) of 12 hours.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients. Activity transfer coefficients are based on data from the Agricultural Re-entry Task Force (ARTF). Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value of 25% of the application rate with a daily dissipation value of 10% was used in the exposure assessment.

Exposure estimates were compared to the toxicological end point to obtain the margin of exposure (MOE); the target MOE is 100. Dermal risks to workers were not of concern (MOEs were above the target MOE; Appendix I, Table 11) except for hand girdling of table grapes where a 24 hour REI had to be established.

### **3.4.3 Residential Exposure and Risk Assessment**

#### **3.4.3.1 Bystander Exposure and Risk**

Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature, application equipment and sprayer settings. Therefore, bystander exposure should be minimal.

### **3.5 Food Residues Exposure Assessment**

#### **3.5.1 Exposure from Drinking Water**

##### **3.5.1.1 Concentrations in Drinking Water**

Estimated environmental concentrations (EECs) of flupyradifurone in potential drinking water sources (groundwater and surface water) were calculated using computer simulation models. EECs of flupyradifurone in groundwater were calculated using the PRZM-GW model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using PRZM-GW are averaged concentrations in the top 1 m of the saturated zone (aquifer). EECs of flupyradifurone in surface water were calculated using the PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body (a small reservoir) and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a small reservoir only.

The flupyradifurone transformation product difluoroacetic acid (DFA) was also modelled, taking into account the calculated fraction of applied flupyradifurone which is expected to transform to DFA, as it has the same magnitude for health concerns as its parent. The aquatic phototransformation products, azabicyclosuccinamide (M47) and BYI 02960-succinamide (M48), appeared to be persistent in water. Very little information is available regarding their environmental and health concerns, and therefore, to be conservative, they were included in the screen level modelling for drinking water from sources of surface water.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate. Twenty six initial application dates between April and September were modelled. The model was run for 50 years for all scenarios. The largest EECs of all selected runs are reported in Table 3.5.1-1 below for both flupyradifurone and DFA. Modelling for drinking water derived from surface water used a phototransformation rate constant for flupyradifurone with two phototransformation products, M47 and M48, so the flupyradifurone EECs for surface water in Table 3.5.1-1 can be considered to include these two compounds.

**Table 3.5.1-1 Level 1 estimated environmental concentrations of flupyradifurone and DFA in potential drinking water sources**

Compound	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)	
			Reservoir	
	Daily <sup>1</sup>	Yearly <sup>2</sup>	Daily <sup>3</sup>	Yearly <sup>4</sup>
Flupyradifurone (FPD) <sup>5</sup>	167	165	26	6.5
DFA <sup>6</sup>	115	114	6.7	1.6
FPD + DFA	267	264	31	7.1

1 90<sup>th</sup> percentile of daily average concentrations

2 90<sup>th</sup> percentile of yearly average concentrations

3 90<sup>th</sup> percentile of yearly peak concentrations

4 90<sup>th</sup> percentile of yearly average concentrations

5 Surface water EECs include phototransformation products M47 and M48

6 As parent equivalent concentration. Actual concentration would be one third this amount.

### 3.5.2 Residues in Plant and Animal Foodstuffs

According to the nature of the residue studies (plant, high-temperature hydrolysis, confined crop rotation, and livestock), parent flupyradifurone was the major residue in foods for human consumption. Based on this, flupyradifurone per se is considered an appropriate marker for primary crops, processed commodities, rotational crops, and livestock matrices, and is recommended as the residue definition for enforcement purposes. Given the comparable toxicities of parent and DFA and the relative amounts of both found in plant metabolism, secondary crops and crop field trials, the sum of flupyradifurone and DFA, expressed as parent equivalents, is the recommended residue definition for commodities of plant origin for dietary exposure assessment. The proposed residue definitions for enforcement and risk assessment are consistent with those of the USEPA.

HPLC-MS/MS methods were developed for data gathering and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the LOQ (0.01 ppm for each analyte) in plant and livestock matrices. The demonstrated storage stability intervals cover the actual intervals of frozen storage for plant and livestock commodity samples (-20°C) from crop field trials, processing, and livestock feeding studies. Therefore, no



corrections for loss of residues during storage are required. An adequate number of residue trials with acceptable geographical distribution were submitted on a range of representative commodities of various crop groups (CG), namely 1B, 1C, 3-07, 4-13, 5-13, 6A, 6B, 6C, 8-09, 9, 11-09, 13-07B, 13-07F, 13-07G, 14-11, 22B, field corn, popcorn grain, sweet corn kernels plus cob with husks removed, dry soybeans, and peanuts to allow the establishment of MRLs. Sufficient residue trials were conducted in/on imported commodities (10-Revised, CG15 (except rice and field corn, popcorn grain, and sweet corn plus cob with husks removed), 20C, green coffee beans, hops (dried), prickly pears, and prickly pear pads) according to the critical good agricultural practice (GAP) and applicable guideline requirements, providing data appropriate for setting import MRLs. Based on processing studies, a separate MRL is only necessary for raisins as the anticipated residue of flupyradifurone (4.7 ppm) exceeds the proposed MRL (3.0 ppm) for the crop subgroup 13-07F. All of the proposed MRLs in food crops are aligned with the US Tolerances, with exception of revised crop group descriptors (CGs 4-13, 5-13, and 22B).

Feedstuff items associated with proposed domestic uses in Canada are alfalfa, almonds, apples, carrots, corn, peas, beans, potatoes, and soybeans. Anticipated residues in animal matrices are all below the LOQ for poultry matrices. However, in ruminant matrices, residues of flupyradifurone are quantifiable in swine matrices, and dairy cattle matrices, which are extended to goats, horses, and sheep.

### **3.5.3 Dietary Risk Assessment**

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.16), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

#### **3.5.3.1 Chronic Dietary Exposure Results and Characterization**

The following criteria were applied to the refined chronic non-cancer analysis for flupyradifurone and DFA, expressed as parent equivalents: 100% crop treated, anticipated residues in processed fractions (where available), supervised trial median residue values, anticipated residues for all animal commodities, and a Level 1 estimated environmental concentration of flupyradifurone and DFA in potential sources of drinking water. The refined chronic dietary exposure from all supported flupyradifurone food uses (alone) is 15% (0.012108 mg/kg bw/day) of the ADI for children 1 to 2 years of age (highest exposed subpopulation). Aggregate exposure from food and drinking water is considered acceptable for all subpopulations. The PMRA estimates that the refined chronic dietary exposure to flupyradifurone and DFA, expressed as parent equivalents, from food and drinking water is 31% (0.024633 mg/kg bw/day) of the ADI for infants less than 1 year, the highest exposure subpopulation.

The following assumptions were applied in the refined acute analysis for flupyradifurone and DFA, expressed as parent equivalents: 100% crop treated, highest average field trial (HAFT) values were used for blended (B) commodities, maximum residue values for partially blended (PB) and non-blended (NB) commodities, anticipated residues in processed commodities (where

available), anticipated residues in animal commodities, and a Level 1 estimated environmental concentration of flupyradifurone and DFA in potential sources of drinking water. The refined acute dietary exposure (food alone) for all supported flupyradifurone food uses is estimated to be 21.6% (0.075646 mg/kg bw/day) of the ARfD in children 1 to 2 years of age, the highest exposed subpopulation (95<sup>th</sup> percentile, deterministic), and 16.7% (0.021766 mg/kg bw/day) of the acute reference dose for females 13 to 49 years of age. The refined aggregate exposure from food and drinking water is considered acceptable for females 13 to 49 years of age at 24% (0.031229 mg/kg bw/day) of the ARfD. The highest exposure and risk estimate is for children 1 to 2 years of age at 25.5% (0.089301 mg/kg) of the ARfD.

### 3.5.4 Aggregate Exposure and Risk

The aggregate risk for flupyradifurone consists of exposure from food and drinking water sources only; there are no residential uses.

### 3.5.5 Maximum Residue Limits

**Table 3.5.5.1 Proposed Maximum Residue Limits**

<b>Food Commodity</b>	<b>Recommended MRL (ppm)</b>
<i>Brassica</i> leafy greens (CG4-13B)	40
Leafy greens (CG4-13A)	30
Hops (dried)	10
Leaf petioles vegetables (CG22B)	9.0
<i>Brassica</i> head and stem vegetable group (CG5-13)	6.0
Raisins	5.0
Bushberry (CG13-07B, except highbush cranberries)	4.0
Green onions (CG3-07B)	3.0
Citrus fruits (revised) (CG10-R)	3.0
Edible-podded legume vegetables (CG6A)	3.0
Small fruit vine climbing subgroup (CG13-07F, except fuzzy kiwifruit)	3.0
Cereal grains (CG15, except rice, field corn, popcorn grain, and sweet corn kernels plus cob with husks removed)	3.0
Dried shelled pea and bean (CG6C, except soybean)	3.0
Succulent shelled English peas	2.0
Succulent shelled garden peas	2.0
Succulent shelled green peas	2.0
Succulent shelled peas	2.0
Succulent shelled pigeon peas	2.0
Fruiting vegetables (CG8-09)	1.5
Low growing berry (CG13-07G, except lowbush blueberries and cranberries)	1.5

<b>Food Commodity</b>	<b>Recommended MRL (ppm)</b>
Dry soybeans	1.5
Green coffee beans	1.5
Root vegetable (CG1B, except sugar beet)	0.9
Undelinted cotton seeds (CG20C-R)	0.8
Pome fruits (CG11-09)	0.7
Prickly pear pads	0.7
Meat byproducts of cattle, goats, horses, and sheep	0.5
Cucurbit vegetables (CG9)	0.4
Prickly pears	0.3
Succulent shelled blackeyed peas	0.2
Succulent shelled broad beans	0.2
Succulent shelled cowpeas	0.2
Succulent shelled lima beans	0.2
Succulent shelled southern peas	0.2
Meat of cattle, goats, horses, and sheep	0.15
Bulb onions (CG3-07A)	0.09
Fat of cattle, goats, horses, and sheep	0.06
Milk	0.06
Tuberous and corm vegetables (CG1C)	0.05
Field corn, and popcorn grain	0.05
Sweet corn kernels plus cob with husks removed	0.05
Peanuts	0.04
Meat byproducts of hogs	0.02
Tree nuts (CG14-11)	0.02
Fat, meat and meat byproducts of poultry	0.01
Eggs	0.01
Fat and meat of hogs	0.01

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the [Residue Chemistry Crop Groups](#) webpage in the Pesticides and Pest Management section of Health Canada's website.

For additional information on Maximum Residue Limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 9 and 10.



## 4.0 Impact on the Environment

### 4.1 Fate and Behaviour in the Environment

Based on physico-chemical properties, flupyradifurone is soluble in water, is not likely to volatilize from moist soil or water surfaces under field conditions, and it has low potential for long-range transport in the atmosphere. Flupyradifurone is not expected to bioaccumulate in organisms.

Under the Canadian temperate climate, flupyradifurone is moderately persistent to persistent in aerobic soils and persistent in anaerobic (flooded) soils, and has a potential to be carried over to the following growing season. The primary dissipation route of flupyradifurone is aerobic biotransformation, forming CO<sub>2</sub> and two other major transformation products: 6-chloronicotinic acid (6-CNA) and difluoroacetic acid (DFA). 6-CNA is of transient nature and is non-persistent; while DFA degrades more slowly and is moderately persistent. Observations from terrestrial dissipation studies are consistent with the laboratory results.

Flupyradifurone sorbs weakly to soil constituents and the process is partially reversible. It is considered mobile and has the potential to leach to groundwater based on the criteria of Cohen *et al.* (1984) and the leaching criteria of the ground water ubiquity score (GUS) (Gustafson, 1989); both considered persistence (aerobic soil biotransformation half-lives) and organic-carbon partition coefficients ( $K_{oc}$ ). This is supported by its intrinsic physico-chemical properties (high aqueous solubility and low log  $K_{ow}$ ), the results of laboratory studies, as well as water modelling results. However, in terrestrial field dissipation studies, flupyradifurone was not detected in soil below 30-cm in depth.

In the aquatic environment, flupyradifurone is expected to distribute relatively evenly between water and sediment phases due to its high solubility and low tendency to partition in organic substances (low log  $K_{ow}$ ). A laboratory study suggests that the adsorption of flupyradifurone to soil is a time dependant process, and thus, it is reasonable to expect that concentration of flupyradifurone in the water layer will decrease over time by forming bound residues in the sediment. Flupyradifurone is stable to hydrolysis and persistent to biotransformation under aerobic and anaerobic conditions. However, it can be phototransformed in water, forming two major transformation products, BYI 02960-succinamide and azabicyclosuccinamide. The fate of the phototransformation products are unknown; however, formation of these products would be limited to clear shallow waters. The major route of dissipation in the aquatic environment is likely to be dilution through water movement because it is highly soluble and persistent. Phototransformation in the clear shallow water can also be an important route of dissipation.

A summary of environmental fate data is presented in Appendix I, Table 12.

## 4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse ecological effects. This integration is achieved by comparing exposure concentrations (i.e. the expected environmental concentration (EEC)) with concentrations at which adverse effects occur (i.e. toxicity endpoints such as  $LC_{50}$ ,  $LD_{50}$ , NOEC or NOEL). For characterizing acute risk, acute toxicity values (for example,  $LC_{50}$ ,  $LD_{50}$ , and  $EC_{50}$ ) are divided by an uncertainty factor. The uncertainty factor is used to account for differences in inter- and intra-species sensitivity as well as varying protection goals (for example, community, population, individual). Thus, the magnitude of the uncertainty factor depends on the group of organisms that are being evaluated (for example, 10 for fish, 2 for aquatic invertebrates). The difference in value of the uncertainty factors reflects, in part, the ability of certain organisms at a certain trophic level (i.e. feeding position in a food chain) to withstand, or recover from, a stressor at the level of the population. When assessing chronic risk, the NOEC or NOEL is used and an uncertainty factor is not applied.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value ( $RQ = \text{exposure/toxicity}$ ), and the RQ is then compared to the level of concern ( $LOC = 1$  for most species, 0.4 for pollinators and 2 for beneficial arthropods (acute screening tests for predatory mite and parasitoid wasp)). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

The risk of flupyradifurone and its related end-use products to organisms was assessed based upon the maximum annual application rate of 400 g a.i./ha, applied either as a single soil application or as two spray applications of 200 g a.i./ha with 7 days interval when using Sivanto 200 SL and the maximum label rate of 37.75 g a.i./ha per season for soybean seed treatment when using BYI 02960 480 FS. The most sensitive endpoints were selected for the screening level risk assessment and uncertainty factors were applied.

Because the seed treatment rate is much lower than foliar and soil application rates and because exposure from seed treatment to aquatic environments is minimal, the risk assessment for seed treatment use will be limited for bees, birds and mammals only.

A summary of EEC values used for the screening level risk assessment is presented in Appendix I, Table 13. Summaries of all available ecotoxicity data are presented in Appendix I, Tables 14, 15 and 16.

#### **4.2.1 Risks to Terrestrial Organisms**

A risk assessment of flupyradifurone and its end use products Sivanto 200 SL and BYI 02960 480 FS was undertaken for terrestrial organisms based on available toxicity data for earthworms, bees and other beneficial arthropods, birds, small wild mammals and terrestrial plants. At the screening level, EECs are calculated for direct on-field application for all terrestrial organisms. During refined risk assessment, off-field EECs resulting from drift were considered. The percent off-field drift considered for Sivanto 200 SL was 11%, 74%, and 26%, for ground spray, early airblast and aerial application, respectively.

##### **Terrestrial invertebrates**

As an insecticide, toxicity of flupyradifurone to non-target invertebrates is expected. Consequently a number of toxicity studies were conducted with several species including earthworms, foliar and soil-dwelling predators and bees at different tiers. These studies are summarized in Appendix I, Tables 14 and 15.

##### **Earthworms and soil dwelling arthropods**

Earthworms: To assess the toxicity to earthworms (*Eisenia fetida*), acute and chronic laboratory studies as well as a field study were conducted. Mortality was observed in the acute laboratory studies with flupyradifurone, the formulated product Sivanto 200 SL, whereas no mortality was observed for the major soil transformation products difluoroacetic acid (DFA) and 6-chloronicotinic acid (6-CNA). The corresponding LC<sub>50</sub> values were 213.2 mg a.i./kg soil (dry weight (dw)), 709 mg product/kg dw soil (equivalent to 121 mg a.i./kg dw soil), > 1000 mg DFA/kg dw soil, and > 1000 mg 6-CNA/kg dw soil, respectively (Appendix I, Table 14). On chronic basis, effects on juvenile growth and survival were observed. The NOEC values for Sivanto 200 SL, DFA and 6-CNA were 8.9 (equivalent to 1.5 mg a.i.), 62 and 95 mg/kg dw soil, respectively. The results from the field study showed that there was no unacceptable adverse effects on abundance and biomass of total earthworm population at 1500 g a.i./ha, more than three times of the maximum annual application rate.

At the screening level, the EEC was calculated by assuming a maximum soil application rate of 400 g a.i./ha, a soil bulk density of 1.5g/cm<sup>3</sup> and a soil depth of 15 cm, resulting in an EEC of 0.18 mg a.i./kg soil. Using the most sensitive LC<sub>50</sub> of 121 mg a.i./kg dw soil and NOEC of 1.5 mg a.i./kg dw soil, RQ is < 0.2 for both, indicating risk for acute and chronic adverse effects does not exceed the level of concern for earthworms (LOC <1) (Appendix I, Table 17).

Soil-dwelling arthropods: To assess the toxicity on soil-dwelling arthropods (represented by soil mite (*Hypoaspis aculeifer*), springtail (*Folsomia candida*) and rove beetle (*Aleochara bilineata*)), chronic laboratory studies were conducted with Sivanto 200 SL, DFA and 6-CNA. No adverse effects were observed for soil mites and rove beetles with any of the test substances. However,



for springtail, adverse effects on adult mortality and reproduction were observed for Sivanto 200 SL and 6-CNA, but not for DFA. A summary of all the endpoints derived from these studies is presented in Appendix I, Table 14.

The screening level risk assessment was conducted using  $ER_{50}$  of  $> 300$  g a.i./ha ( $> 0.12$  mg a.i./kg dw soil) for the most sensitive organism and a maximum soil application rate of 400 g a.i./ha, resulting in a RQ of  $< 1.33$  (Appendix I, Table 17), indicating a potential risk to soil-dwelling arthropods ( $LOC > 1$ ). However, given that the level of concern is only slightly exceeded and that there were no observed effects at the concentration tested the risk to terrestrial arthropods is deemed to be negligible.

When considering off-field exposure due to spray drift scenarios based on application methods, the off-field EECs are reduced to 44, 296 and 104 g a.i./ha, respectively, for ground spray (11%), early airblast (74%) and aerial application (26%). Correspondingly, RQ values are 0.15, 0.99 and 0.35, respectively (Appendix I, Table 17). Therefore, level of concern is not exceeded, suggesting that the potential risk to this group of organisms is negligible and the population is likely to recover within a reasonable time period.

### **Beneficial foliage-dwelling arthropods**

To assess the toxicity on foliar-dwelling arthropods, acute and extended laboratory studies, semi-field and field studies were conducted with Sivanto 200 SL (Appendix I, Table 14).

Screening level: Initial studies were conducted with the indicator species, *Aphidius rhopalosiphii* and *Typhlodromus pyri*, whereby insects were exposed to residues of flupyradifurone (applied as Sivanto 200 SL) on glass plates for 2 to 7 days. Mortality was observed for both species.  $LR_{50}$  was determined to be  $< 0.5$  g a.i./ha and 17 g a.i./ha, respectively. At a foliar application rate of  $2 \times 200$  g a.i./ha with 7 days interval and assuming a foliar half-life of 10 days, the screening level EEC for direct over spray is 323 g a.i./ha. Therefore, the corresponding RQ values are  $> 646$  and 19 (Appendix I, Table 18), indicating that flupyradifurone has the potential to pose a risk to foliar-dwelling arthropods based on the screening level assessment, and a refined assessment is needed.

When considering the off-field scenarios, the EECs calculated for ground spray, early airblast and aerial applications were 35.5, 239 and 84 g a.i./ha, respectively (Appendix I, Table 13). Therefore, the RQ values for parasitoid wasp are  $> 142$ ,  $> 956$  and  $> 336$ , and the RQ values for predatory mite are 2.1, 14.1 and 4.95, respectively, all exceeding the LOC (Appendix I, Table 18).

Tier I refined risk characterization: The tier I refinement considers the toxicity endpoints obtained from extended tests through exposure of *A. rhopalosiphii* and *T. pyri* on treated leaf surfaces for 2 and 14 days. Mortality was observed for both species and the corresponding  $LR_{50}$  values were 2.02 g a.i./ha for *A. rhopalosiphii* (2 days) and 177 g a.i./ha for *T. pyri* (14 days). Using the same in-field and off-field EECs, RQ values are calculated (Appendix I, Table 18). Though the LOC is still exceeded when using the  $LR_{50}$  value obtained from the 2-day extended test (*A. rhopalosiphii*), exposure under early airblast drift scenario is the only case where the RQ

exceeds 1 (1.35) when using the  $LR_{50}$  value obtained from the 14-day extended test with *T. pyri* (Appendix I, Table 18). The foliar-dwelling ladybug (*Coccinella septempunctata*) and the soil-dwelling rove beetle (*Aleochara bilineata*) were also tested under extended laboratory conditions. For these two species, the LOC was exceeded only from in-field exposure (Appendix I, Table 18).

Tier II refinement: To further examine the potential effects of flupyradifurone to beneficial insects, a tier II refinement was performed taking into consideration a three-dimensional structure as well as results from semi-field and field studies. For exposure in a three-dimensional structure, EECs are adjusted by considering foliar deposition factors which account for interceptions by the crop (for in-field exposure) or the off-field vegetation (for off-field exposure).

For the in-field exposure estimate, it assumes that the foliar deposition fraction ( $F_{int}$ ) plus the soil deposition fraction ( $F_{soil}$ ) is unity ( $F_{int} + F_{soil} = 1$ ), and that the deposition and interception occur instantaneously (Linders *et al.*, 2000). As Sivanto 200 SL is proposed for registration on a variety of crop groups, the selection of a single foliar and soil deposition factors was not possible. Three foliar deposition factors were then selected to represent various crops and timing of seasonal growth: 0.3, 0.5, and 0.7. Calculations under these scenarios resulted in RQ values ranging from 0.35 to 112 for foliar dwelling organisms, indicating that even with this refinement, there is still a risk to some species in this group of organisms (Appendix I, Table 19).

For the tier II off-field exposure estimate, a vegetation distribution factor of 0.10 was applied since the drift values overestimate drift to the lower or interior portions of a three-dimensional habitat structure. Most of the drift would be intercepted by the top or side portions of the habitat structure. This default value was estimated to be appropriate based on data presented at the ESCORT workshop (Candolfi *et al.*, 2001). Thus, the refined off-field EEC for the drift scenarios of ground spray, early airblast and aerial applications are 3.55, 23.9 and 8.4 g a.i./ha, respectively (Appendix I, Table 19). For *A. rhopalosiphi* with the toxicity endpoint  $LR_{50}$  of 2.02 g a.i./ha obtained from a 48-hour extended test, off-field risk quotients are all still over the LOC, ranging between 1.76 and 11.8 (Appendix I, Table 19), thus continue to indicate that there is a risk to this group of organisms.

The semi-field studies conducted with parasitoid wasp (*Aphidius rhopalosiphi*) and predatory bug (*Orius laevigatus*) showed that when the organisms were exposed to residues of Sivanto 200 SL ( $2 \times 250$  g a.i./ha with 10 days interval) aged on leaves under semi-field conditions, mortality and reproduction recovered gradually and by day 56 and 42, near 100% recovery was observed for parasitoid wasp and predatory bug, respectively (Appendix I, Table 20).

The field studies capable of assessing toxicity effects at the community and population levels showed that treatment with Sivanto 200 SL in two grassland habitats did not lead to statistically significant effects on prevailing arthropod communities at testing rates of 21 g a.i./ha (Appendix I, Table 20). At the population level, both trials showed reduction of a few taxa in comparison with the controls, however, population rebound was observed. It was concluded that in both studies 21 g a.i./ha can be considered as the no observed ecologically adverse effect rate, which is slightly lower than the refined off-field EEC of 23.9 g a.i./ha from an airblast application, but higher than the refined off-field EECs from ground and aerial applications. Therefore, it can be assumed that recovery of certain species is expected while others may be affected.

## Honeybees

Tier I studies: Acute toxicity testing with young adult bees indicated that flupyradifurone is practically non-toxic to honeybees on an acute contact exposure basis ( $LD_{50} > 122.8 \mu\text{g a.i./bee}$ ); however, the compound is categorized as highly toxic to bees on an acute oral exposure basis ( $LD_{50} = 1.2 \mu\text{g a.i./bee}$ ). Repeated exposure of individual adult bees over 10 days to sucrose solutions containing up to 10,000  $\mu\text{g a.i./L}$  (equivalent to a dose of 0.464  $\mu\text{g a.i./bee/day}$ ) did not result in an adverse effect; repeated exposure of bee larvae to diets containing 10,000  $\mu\text{g a.i./kg}$  diet (equivalent to a dose of 0.55  $\mu\text{g ai/larvae/day}$ ) did not result in an adverse effect on survival or adult emergence after 21 days (Appendix I, Table 15).

Acute contact and oral studies were also conducted with the foliar, soil and seed treatment end-use product formulations, as well as transformation products. Oral toxicity studies with seed treatment formulation (BYI 02960 480 FS) and soil/foliar formulation (Sivanto 200 SL) indicated that they were moderately toxic to adult bees ( $LD_{50}$  of 3.4  $\mu\text{g a.i./bee}$  for the seed treatment application and an  $LD_{50}$  of 3.2  $\mu\text{g a.i./bee}$  for the soil/foliar formulation). Contact exposure to both formulations were practically non-toxic (96-hour  $LD_{50}$  of 68.6  $\mu\text{g a.i./bee}$  for the seed treatment formulation and 72-hour  $LD_{50}$  of 15.7  $\mu\text{g a.i./bee}$  for the soil/foliar formulation). Oral and contact exposure studies with transformation products (difluoroethyl-amino-furanone, hydroxy, difluoroacetic acid (DFA), 6-chloronicotinic acid (6-CNA) and 6-chloro-picolylalcohol) indicated they were all practically non-toxic to bees (Appendix I, Table 15).

When the formulated product Sivanto 200 SL was mixed with the tebuconazole formulation EW 250C G (17% tebuconazole), the toxicity of flupyradifurone to young adult honeybees increased by 15.7-fold and 16.0-fold via the contact and oral exposure routes, respectively (Appendix I, Table 15). This data indicate that the combination of the two actives can enhance the toxicity of flupyradifurone and that a similar effect may be possible when flupyradifurone is used in combination with other azole fungicides that have similar mode of action.

For foliar applications, based on the initial screening level exposure estimates (Appendix I, Table 21) and refined (i.e. measured residues in pollen and nectar, Appendix I, Table 22), tier I RQ values for bees (adult and brood) exceeded the acute and chronic risk LOCs of 0.4 and 1.0, respectively, on an oral exposure basis, but no potential risks of concern were identified on an acute contact exposure basis (Appendix I, Tables 21 and 22). There is negligible risk to bees from oral exposure to residues in pollen and nectar from soil and seed treatments, and from pre-



bloom foliar applications (i.e. negligible risk from residues translocated into pollen and nectar) based on generic screening-level exposure estimates (USEPA, 2012). The screening-level analysis, therefore, indicates that the primary concern for bee pollinators is through the consumption of residues in pollen and nectar and not through contact exposure. These potential risks from oral exposure apply to both foraging worker bees, nurse bees and larvae (i.e. brood). Therefore, the higher tiered honeybee studies are considered to further evaluate the potential adverse effects of flupyradifurone foliar applications at the colony or population level.

Tier II and III studies: Available semi-field and field studies consisted of studies where flupyradifurone was fed directly to colonies, or studies where bees were allowed to forage on residues following multiple applications of the compound at the maximum label rate, including foliar applications at full bloom while bees were actively foraging. These studies indicated that there were some transitory effects on honeybee mortality and foraging activity at periods following applications at full bloom while bees were foraging (Appendix I, Table 23). The available data also indicate that the majority of flupyradifurone residues measured in plants were in pollen as opposed to nectar (although cotton is an exception). Residue data for bee-relevant matrices (i.e. pollen, nectar) from crop residue and field studies generally indicate that the highest residues occur immediately after foliar applications, especially at full bloom, when bees are most likely to be visiting the treated area. This is also the time period when transitory effects on mortality and foraging were identified in some of the higher tiered honeybee studies. There is, however, no evidence from the available studies that any of these transitory effects resulted in detectable effects to colony development (including colony health, brood development and food storage, colony weight), overall colony vitality or overwintering success (Appendix I, Table 23).

The most conservative exposure scenario occurred in the two field studies (PMRA numbers 2236673 and 2236675) in which oil-seed rape seeds were treated with BYI 02960 480 FSseed treatment, sown into soil treated with (310 g a.i./ha) Sivanto 200 SL, and then plants were later treated with two foliar applications (205 g a.i./ha each) of Sivanto 200 SL, including one application at full bloom. These studies generally did not indicate adverse effects related to a range of endpoints including adult foraging activity, colony strength, brood development and overwintering success. However, based on pollen analysis it appeared that some bees in these studies were foraging on alternative (non-oil seed rape) food sources (oil seed rape pollen in samples ranged from approximately 20 – 70%). However, such a situation would most likely occur under any application scenario (Appendix I, Table 23).

In addition, because of the low acute contact toxicity ( $LD_{50} > 122.8 \mu\text{g a.i./bee}$ ) foraging worker bees are not expected to be at risk from contact exposure to contaminated dust generated from seeding equipment following applications of flupyradifurone. Oral exposure resulting from dust-off is not expected to be significantly greater than that resulting from foliar application to blooming crops while bees are foraging. Results of the semi-field and field studies demonstrated minimal oral and contact toxicity effects following multiple applications (including foliar applications while bees were foraging), suggesting minimal effects would be expected from oral exposure to dust-off during planting where exposure is expected to be similar or less. Furthermore, a screening level assessment based on the 2013 EFSA guidance indicated that risk is not expected for adults or larva from contact or oral exposure to dust from planting of treated seed.

In conclusion, the collective results of the laboratory, semi-field and field studies indicate that effects from direct spray application at the maximum rate to blooming crops while bees are actively foraging are transient (increased mortality and decreased foraging activity), with no long-term effect on colony through overwintering. There is negligible risk from contact exposure to flupyradifurone based on the negligible contact toxicity, the extended residue study, and the semi-field and field studies. Furthermore, dust-off during planting of treated soybean seeds is expected to pose minimal risk due to the negligible contact toxicity and low risk from oral exposure. In order to minimize any transient effects on honeybee colonies, and minimize any effects to native pollinators that may include solitary bees, it is recommended that foliar applications be made in the early morning or evening when most bees are not actively foraging. Exposure from drift should also be mitigated.

Finally, due to observed increase in toxicity to young adult honeybees via the contact and oral exposure routes when Sivanto 200 SL was mixed with the tebuconazole formulation EW 250C G, it is recommended that products containing flupyradifurone should not be tank mixed with azole fungicides during bloom period.

### **Birds and mammals**

Flupyradifurone and the formulation product Sivanto 200 SL are moderately toxic to Northern bobwhite quail (*Colinus virginianus*), canary (*Serinus canaria*) and practically non-toxic to chicken (*Gallus gallus domesticus*) on an acute oral exposure basis and slightly toxic to bobwhite quail and mallard duck (*Anas platyrhynchos*) on a dietary exposure basis. Mortality was observed in the acute oral tests but not in the dietary tests. Other effects included reductions in feed consumption, body weight and body weight gains. The acute oral LD<sub>50</sub> was 232 (95% CI = 173–313) mg a.i./kg bw when tested with flupyradifurone TGA1 and 459 (95% CI = 339 – 616) mg a.i./kg bw when tested with Sivanto 200 SL for bobwhite quail, 330 (95% CI = 215 – 625) mg a.i./kg bw for canary and > 2000 mg a.i./kg bw for chicken (Appendix I, Table 14). Flupyradifurone TGA1 appears to be more toxic to birds than Sivanto 200 SL formulation. The dietary LD<sub>50</sub> was > 470 mg a.i./kg bw/day for bobwhite quail and > 825 mg a.i./kg/day for mallard duck (Appendix I, Table 14).

Chronically, no treatment-related adverse effects on reproductive parameters or on the parental generations were observed for mallard duck up to the highest concentration tested (NOAEC = 845 mg a.i./kg diet) during a 20-week dietary exposure study (Appendix I, Table 14). However, there is some uncertainty surrounding this study since adverse growth effects were observed at concentrations >1175 mg a.i./kg diet in the acute dietary study with mallard ducks, although no effects to parental growth were reported in the reproduction study. In contrast, in a 23-week reproduction study with the bobwhite quail, statistically significant ( $p < 0.05$ ) effects were observed at the highest concentration tested (999 mg a.i./kg-diet), including parental survival and female body weight gain, as well as several reproductive parameters. The NOAEC for both parental toxicity and reproduction endpoints is 302 mg a.i./kg diet, equivalent to 40 mg a.i./kg bw/day (Appendix I, Table 14).

Based on the available data, flupradifurone is slightly toxic to small mammals (rats) on an acute oral basis with the most sensitive LD<sub>50</sub> of 300 mg a.i./kg bw. In a rat two-generation reproduction study, the most sensitive effects were decreased body weights and body weight gains in F2 pups at 32 mg/kg bw/day, resulting in an offspring NOAEL of 7.8 mg/kg/day. Some reproductive effects, including decreased sperm counts and litter size, occurred at higher dietary concentration (120 mg/kg bw/day), resulting in a reproductive NOAEL of 32 mg/kg bw/day (Appendix I, Table 14).

Birds and mammals may be exposed to flupyradifurone following the ingestion of plant materials and insects sprayed with flupyradifurone during foliar application or ingestion of insects exposed to flupyradifurone during soil application. Birds and mammals may also be exposed to flupyradifurone through ingestion of treated soybean seeds from application of BYI 02690 480 FS. Thus these three exposure scenarios were considered in the risk assessment.

The screening level risk assessment for Sivanto 200 SL is conducted for direct on-field exposure, the most conservative scenario. Concentrations of flupyradifurone on different food guilds (EDE) are calculated based on either  $1 \times 400$  g a.i./ha for soil application or  $2 \times 200$  g a.i./ha for foliar application with a 7-day interval and a foliar half-life of 10 days. For soil application, risk is identified for small and medium sized insectivorous birds on acute oral basis and for small, medium and large sized insectivorous mammals on a reproduction basis. RQ values calculated using the maximum nomogram residues ranging between 1.1 and 2.4 (Appendix I, Table 24), exceeded the level of concern. When considering mean nomogram residues, RQ values decreased to below 1 for birds but remained above 1 (1.47-1.68) for small and medium sized mammals. Further characterization of the risk to mammals considered off-field exposure scenarios. The potential risk to insectivorous mammals were negligible when applied by ground spray or aerial applications, but a risk remained for early airblast with RQ ranging between 1.1 and 1.2 (Appendix I, Table 24).

For foliar application, risk was only identified for small sized insectivorous birds on acute oral basis (RQ = 1.13) when on-field exposure with maximum nomogram residues was considered. For small wild mammals, on the other hand, risk was identified for both herbivores and insectivores when on-field exposure was considered on the reproduction basis. RQ ranged between 1.2 and 3.8 at maximum nomogram residues for all three sizes of mammals and 1.2 and 1.4 at mean nomogram residues only for small and medium sized mammals (Appendix I, Table 25). Under off-field scenarios, RQ values decreased to below 1 for ground and aerial applications but remained above 1 (RQ of 1.3–2.8 at maximum nomogram residues for all sizes and 1.0 at mean nomogram residues for both small and medium sized mammals).

Overall, because the likelihood for birds and mammals to only consume contaminated food items is very low and the predicted RQs only slightly exceeded the LOC, the risk to these animals is likely to be minimal.

For the seed treatment product BYI 02960 480 FS, the screening level risk assessment uses a conservative approach by assuming that the daily diet of birds and mammals consists of 100% seeds treated at the maximum application rate of 0.068 mg a.i./soybean seed as indicated in the proposed label. The calculated RQ showed that under this conservative assumption, a risk to



small and medium sized birds and mammals was identified on acute oral, dietary and reproduction bases. A risk to large sized mammals was also identified. The RQ values ranged from 0.42 to 3.7 for birds and from 0.78 to 6.4 for mammals (Appendix I, Table 26). It is noted that small birds (for example, chickadee) and small mammals (for example, shrew) are not expected to consume soybean seeds due to the large size of the seed or feeding habits. It is also noted that medium sized birds would have to consume between 34 and 69 seeds per day (depending on the endpoint considered, Appendix I, Table 26) to reach a level of flupyradifurone that would compare to levels represented by the toxicity endpoints. Therefore, the risk to birds is considered low. The number of seeds need to be consumed per day to result in adverse acute and reproduction effects are 441 and 113, respectively, for large sized mammals but as few as 15 and 4 seeds, respectively, for medium sized mammals (Appendix I, Table 26). Therefore, it is concluded that there is a risk concern for wild mammals when flupyradifurone is used for soybean seed treatment.

### **Non-target terrestrial vascular plants**

The toxic effects of flupyradifurone on vegetative vigour and seed emergence of terrestrial vascular plants were tested at the maximum application rate of 410 g a.i./ha. Results showed that inhibition of seedling emergence, survival, shoot length and shoot dry weight did not exceed 25% in any of the seven dicotyledonous and four monocotyledonous species tested. In vegetative vigor study, there were no adverse effects on survival in all the species tested, however, slight visual phytotoxicity was observed. Inhibition in shoot length and shoot dry weight was below the 25% effect in all the species tested.

A screening level assessment was conducted for Sivanto 200 SL using the on-field maximum application rate of 400 g a.i./ha and  $EC_{25}$  of >410 g a.i./ha for seedling emergence and vegetative vigour. In both cases, RQ values are < 1 (Appendix I, Table 27), suggesting that there is a negligible risk to non-target terrestrial plants.

### **4.2.2 Risks to Aquatic Organisms**

Aquatic organisms can be exposed to flupyradifurone as a result of spray drift and runoff. To assess the potential for adverse effects, screening level EECs in the aquatic environment were calculated based on a direct application of 400 g a.i./ha to a 15 cm deep water body representing a seasonal pond suitable for amphibians and an 80 cm deep water body representing a permanent pond. Flupyradifurone was assumed to be instantaneously and completely mixed within the water body. The resulting EECs were 0.27 mg a.i./L for a water body of 15 cm in depth and 0.05 mg a.i./L for a water body of 80 cm in depth (Appendix I, Table 13).

A risk assessment of flupyradifurone was undertaken for freshwater and marine aquatic organisms based on available toxicity data to algae (acute), aquatic plants (acute), invertebrates (acute and chronic), fish (acute and chronic) and amphibians (acute). A summary of aquatic toxicity data for flupyradifurone is presented in Appendix I, Table 16. When calculating RQ values, acute toxicity endpoints ( $E_rC_{50}$  and  $LC_{50}$ ) are divided by an uncertainty factor of 2 for aquatic plants and invertebrates and 10 for fish species. No uncertainty factors are applied to chronic NOEC endpoints.

## Freshwater algae and plants

Acute toxicity to freshwater algae (*Pseudokirchneriella subcapitata*) was performed for flupyradifurone TGAI, formulation product Sivanto 200 SL and three major transformation products DFA (Na salt), BYI 02960-succinamide and 6-CNA (Appendix I, Table 16). No statistically significant ( $p < 0.05$ ) effect on the growth rate of *P. subcapitata* was observed for any of the test chemicals and  $EC_{50}$  were determined to be greater than the highest test concentrations in all tests (Appendix I, Table 16). Screening level RQ was  $< 0.01$ , indicating that flupyradifurone is expected to pose a negligible risk to freshwater algae (Appendix I, Table 28).

Acute toxicity to aquatic vascular plant duckweed (*Lemna gibba*) was determined for flupyradifurone TGAI in a static system. No statistically significant ( $p < 0.05$ ) inhibition on the growth rate of *L. gibba* was observed based on dry weight and front number. The  $EC_{50}$  regarding growth inhibition was determined to be  $> 67.7$  mg a.i./L. A screening level RQ of  $< 0.01$  (Appendix I, Table 28), indicates that the LOC was not exceeded and flupyradifurone poses a negligible risk to freshwater plants.

## Freshwater invertebrates

Both acute and chronic tests on aquatic invertebrates, including *daphnia magna* (water dwelling) and chironomus (sediment dwelling) were performed for flupyradifurone TGAI and Sivanto 200 SL, as well as for metabolites BYI 02960-succinamide, BYI 02960-azabicyclo-succinamide, DFA and 6-CNA (Appendix I, Table 16).

*Daphnia magna*: In the acute toxicity tests on *daphnia magna*, neither immobilisation nor sublethal effects were observed following 48 hours of exposure to flupyradifurone TGAI, DFA and 6-CNA. The 48-hour- $EC_{50}$  was greater than the highest concentration tested for all three substances. When exposed to Sivanto 200 SL at a higher concentration range, however, a dose-response immobilization was observed and the 48-hour- $EC_{50}$  was determined to be 115 mg a.i./L (95% C.I. = 85-179 mg a.i./L). In all cases, the screening level RQ was calculated to be  $< 0.01$  (Appendix I, Table 27), indicating that there is a negligible risk to *daphnia magna* on an acute basis from flupyradifurone even when transformation products were included in EEC estimation.

When *daphnia magna* was exposed to flupyradifurone TGAI on a chronic basis, no mortalities were observed for any treatment level; however, some effects on parental growth and reproductive success were observed. The overall NOEC was determined to be 3.42 mg a.i./L and LOEC was 6.73 mg a.i./L. When *daphnia magna* was exposed to BYI 02960-succinamide on a chronic basis, adverse effect on increased parental age at first offspring emergence was observed at the highest test concentration (106 mg/L). The NOEC was 46.3 mg/L and the LOEC was 106 mg/L. Consequently, the screening level risk quotients were calculated to be 0.015 and 0.001 for flupyradifurone and BYI 02960-succinamide, respectively (Appendix I, Table 28), indicating that there is a negligible risk to *daphnia magna* on a chronic basis.

Chironomus: In the acute toxicity tests on larvae of the midge (*Chironomus riparius*), a dose-response immobilisation was observed following 48 hours of exposure to flupyradifurone TGAI. The EC<sub>50</sub> was calculated to be 63.9 µg a.i./L. When larvae of *C. riparius* were exposed to BYI 02960-succinamide and BYI 02960-azabicyclosuccinamide in a static system for 48 hours, up to 20% of immobilisation was observed at the highest test concentrations. Correspondingly the EC<sub>50</sub> was > 104.5 mg/L and 114.5 mg/L, respectively. The acute effects of 6-CNA to *C. tentans* was only tested at a concentration of 1 mg/L. No mortalities or sublethal effects were observed following 96 hours exposure and therefore, EC<sub>50</sub> was set at > 1 mg/L. When comparing the acute toxicity endpoints, it is clear that flupyradifurone is orders of magnitude more toxic to chironomus than the transformation products.

For an EEC of 0.05 mg a.i./L in an 80 cm deep water body and taking consideration of an uncertainty factor of 2 for acute toxicity endpoint, RQ calculated for the transformation products are all < 0.1, below the level of concern (Appendix I, Table 28). For the parent compound, on the other hand, the resulting RQ is 1.56 (Appendix I, Table 28). Therefore, when applied directly to the water, the risk quotient exceeded LOC. Under spray drift scenarios, RQ reduced to below LOC for ground and aerial applications but remained above LOC (RQ = 1.15) for early airblast application (Appendix I, Table 29).

When *C. riparius* was exposed to flupyradifurone TGAI in a static water-sediment system on a chronic basis, statistical significant ( $p < 0.05$ ) effects on emergence rate and development rate were observed. NOEC was determined to be 10.5 µg a.i./L. Similar toxicity effects were observed when *C. riparius* was exposed to the formulation product Sivanto 200 SL, resulting in a NOEC of 12 µg a.i./L (Appendix I, Table 16). The transformation products DFA and 6-CNA had no chronic effects on *C. riparius*. NOECs were greater than the single test concentration of 105 mg/L for DFA and 102 mg/L for 6-CNA.

Using the most sensitive chronic NOEC value of 10.5 µg a.i./L, the screening level RQ was 4.55, and exceeded the LOC. When exposure through spray drifts was considered, the chronic risk remains under early airblast and aerial application scenarios (Appendix I, Table 29).

Flupyradifurone exposure to aquatic invertebrates through runoff was also considered for five representative regional scenarios of Canada, including BC raspberry, Manitoba potato, Ontario corn, Quebec corn and PEI potato. Using the PRZM/EXAMS models EECs from runoff to a treated field into an adjacent water body consisting of a 1 ha wetland with an average depth of 0.8 m and a drainage area of 10 ha were simulated. The peak concentrations and the average concentrations predicted over a 21 day period (chosen to match the chronic exposure) in the overlying water and pore water in an 80 cm deep water body were used to calculate the risk quotients (Appendix I, Table 30). Results showed that the RQs continued to exceed LOC when chironomus was exposed to flupyradifurone through surface run-off and contaminated pore water (Appendix I, Table 30). Therefore, the use of flupyradifurone poses a potential risk to sediment-dwelling organisms.



## **Freshwater fish and amphibians**

Freshwater fish: Acute toxicity of flupyradifurone to fish was determined with three fresh water species representing a cold water species (rainbow trout (*Oncorhynchus mykiss*)) and two warm water species (fathead minnow (*Pimephales promelas*) and common carp (*Cyprinus carpio*)). Acute toxicity of Sivanto 200 SL and the metabolites BYI 02960-succinamide and DFA to fish was further tested with rainbow trout (Appendix I, Table 16). Chronic toxicity of flupyradifurone to fish was determined in an Early-Life-Stage (ELS) test with fathead minnow.

Following 96 hours of exposure to flupyradifurone TGAI, there were no mortalities or sublethal effects observed at any test concentration for all three fish species, the acute LC<sub>50</sub> was greater than the highest mean-measured concentrations of 74.2 mg a.i./L for rainbow trout, 70.5 mg a.i./L for fathead minnows, and 80 mg a.i./L for common carp (Appendix I, Table 16). When testing with Sivanto 200 SL at a single concentration of 100 mg a.i./L, no effects on common carp were observed; however, rainbow trout showed signs of labored respiration.

In the chronic (ELS) test with fathead minnow, no biologically significant effects were observed on hatchability, larvae survival on day 5, and growth (length and weight). However, there was a statistically significant decrease in fry survival on day 35, which occurred at the highest test concentration. The NOEC was determined to be 4.41 mg a.i./L. In addition, no statistically significant morphological and behavioural effects were observed.

Using the most sensitive acute and chronic endpoints, the screening level RQ values for exposure of flupyradifurone to fish were < 0.02, and did not exceed the LOC (Appendix I, Table 28). Therefore, negligible risk to freshwater fish is expected.

In the acute toxicity tests with rainbow trout the transformation products BYI 02960-succinamide and DFA (Na salt) did not result in mortality or sublethal effects at single mean-measured concentration of 114 and 10.35 mg/L, respectively, over the 96-hour testing period. Therefore, the 96h-LC<sub>50</sub> was determined to be > 114 mg/L BYI 02960-succinamide and >10.35 mg/L DFA. The screening level RQs, calculated by assuming 100% conversions from flupyradifurone, were < 0.15, did not exceed LOC.

Amphibians: Acute toxicity of flupyradifurone to amphibians was determined with African clawed frog tadpoles (*Xenopus laevis*) at a single concentration of 74.2 mg a.i./L. Following 48 hours of exposure, no mortalities or sublethal effects were observed. Therefore, the LC<sub>50</sub> was determined to be >73.8 mg a.i./L. Using an EEC of 0.27 mg a.i./L for a 15 cm deep water body, RQ was calculated to be 0.04 (Appendix I, Table 28), indicating negligible risk to amphibians is expected.

## **Marine/Estuarine species**

Acute toxicity of flupyradifurone to marine/estuarine species was determined with a saltwater fish (sheepshead minnow (*Cyprinodon variegatus*)) and two saltwater invertebrates (Eastern oyster (*Crassostrea virginica*) and mysid shrimp (*Americamysis bahia*)). Mysid shrimp was further tested for effects to early-life cycle.

The acute test on sheepshead minnows showed that flupyradifurone did not cause mortality or sublethal behavioural effects following 96 hours of exposure. The  $LC_{50}$  was  $>83.9$  mg a.i./L, the highest concentration tested. The acute test on the shell deposition of the Eastern oyster showed that flupyradifurone did not cause mortality and nor did it result in significant difference in shell deposition. The  $EC_{50}$  was  $>29$  mg a.i./L, the highest concentration tested.

In contrast, the acute test on mysid shrimp showed that flupyradifurone caused mortality at all test concentrations ranged between 0.12 and 0.98 mg a.i./L following 96 hours of exposure. The  $LC_{50}$  was determined to be 0.25 mg a.i./L. In the ELS study, effects of flupyradifurone on reproduction were observed. These effects included reduction in number of females producing young and mean number of young produced per reproductive day per female. The NOEC for reproduction was determined to be 13.2  $\mu$ g a.i./L.

Based on the EECs estimated for an 80 cm deep water body, the calculated RQ values were below 0.5 for all three marine/estuarine species on an acute basis (Appendix I, Table 28). However, on a chronic basis, RQ for mysid shrimp was 3.85, exceeded LOC. When considering spray drift scenarios, RQ values were reduced to  $< 1$  for ground application and for aerial application on an acute basis. However, RQ remained above 1 for early airblast application (Appendix I, Table 29) and for aerial application on a chronic basis. Further refinement was conducted using modelling results from ecoscenario simulations as described above in the chironomus section. At the peak concentrations and the concentrations predicted for day 21, a risk quotient of 2.27 – 3.64 indicates that the level of concern is exceeded (Appendix I, Table 30). Therefore, flupyradifurone poses a potential risk to sediment-dwelling and marine invertebrates.

#### **4.2.3 Incident Reports**

No incident reports were available. This is a new active ingredient and incident reports are not expected.

### **5.0 Value**

#### **5.1 Effectiveness Against Pests**

A total of 85 efficacy trials were submitted which tested foliar applications of flupyradifurone. These trials demonstrated that foliar applications of Sivanto 200 SL at rates of 500-750 mL/ha control certain aphids, leafhoppers and scale insects and foliar applications of Sivanto 200 SL at rates of 750-1000 mL/ha control whiteflies, Colorado potato beetle and blueberry maggot and suppresses pear psylla (see Appendix I, Table 32).

Twenty-two efficacy trials were submitted which tested soil applications of flupyradifurone. These trials demonstrated that soil applications at rates of 750-1000 mL/10,000 plants controlled aphids, leafhoppers and whiteflies on fruiting vegetables and cucurbit vegetables, and at rates of 1500-2000 mL/ha controlled leafhoppers on berry and small fruit – vine including grapes.

Seed treatment applications of BYI 02960 480 FS were tested in 13 submitted efficacy trials at rates of 13.3-20 mL/140,000 soybean seed. These trials demonstrated that BYI 02960 480 FS protects soybean seedlings against soybean aphid and bean leaf beetle adults (see Appendix I, Table 33).

## **5.2 Phytotoxicity to Host Plants**

Efficacy trials were conducted on a wide variety of outdoor crops with no reports of adverse effects on these plants.

## **5.3 Economics**

No market analysis was done for this application.

## **5.4 Sustainability**

### **5.4.1 Survey of Alternatives**

For most of the supported crop-pest combinations of the two flupryadifurone products there are numerous alternative active ingredients currently registered. Alternative active ingredients include MoA Groups 1 (carbamates, organophosphates), 3A (pyrethroids), 4 (neonicotinoids, sulfoxaflor), 5 (spinosyns), 6 (avermectins), 9 (pymetrozine, flonicamid), 15 (benzoylureas), 17 (moulting disruptors), 21A (pyridaben), 23 (tetronic and teramic acid derivatives) and 28 (diamides), as well as insecticidal soap, mineral oil and silicon dioxide.

There are no alternative active ingredients registered against whiteflies on Crop Group 2 (Leaves of Root and Tuber Vegetables). Flupryadifurone is a new mode of action for use against aphids and leafhoppers on alfalfa.

### **5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management**

BYI 02960 480 FS and Sivanto 200 SL are compatible with most current management practices for the labelled crops and pests.

### **5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance**

Flupryadifurone is an insecticide in a new Mode of Action (MoA) Subgroup (Subgroup 4D, the Butenolides). MoA Group 4 includes the neonicotinoids (Group 4A), nicotine (4B) and sulfoxaflor (4C). There are no recorded incidences of resistance to flupryadifurone in the Michigan State University Arthropod Pesticide Resistance Database. However, there are reports of resistance to some neonicotinoids by certain aphids, whiteflies and flies related to the blueberry maggot, and by the Colorado potato beetle. It is possible that neonicotinoid resistant pests may have cross resistance to flupryadifurone.



#### 5.4.4 Contribution to Risk Reduction and Sustainability

Flupyradifurone represents a new MoA Group for use against aphids and leafhoppers on alfalfa.

Flupyradifurone has been identified as a replacement for diazinon against aphids on pome fruit, radish, rutabaga and turnip, against pear psylla on pear, and against scales on pome fruit. It has also been identified as a replacement for endosulfan against white apple leafhopper on pome fruit, aphids on celery, cucumber, eggplant, head lettuce, melon, peppers, potato, pumpkin, squash, strawberry, and tomato, and leafhoppers and Colorado potato beetle on eggplant, pepper, potato, and tomato.

This active ingredient provides a new MoA Subgroup (Subgroup 4D, the Butenolides) for all of the labelled pest/crop combinations. However, other MoA Group 4 active ingredients are registered for use on many of these pest/crop combinations.

### 6.0 Pest Control Product Policy Considerations

#### 6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, flupyradifurone and its major transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03<sup>5</sup> and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Flupyradifurone does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 31 for comparison with Track 1 criteria.
- Flupyradifurone is unlikely to form any transformation products that meet all Track 1 criteria. See Appendix I, Table 31 for comparison with Track 1 criteria.

---

<sup>5</sup> DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

## 6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*<sup>6</sup>. The list is used as described in the PMRA Notice of Intent NOI2005-01<sup>7</sup> and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,<sup>8</sup> and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances and allergens known to cause anaphylactic-type reactions, are not expected to be present in the technical product flupyradifurone;
- Based on the formulating processes used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances and allergens known to cause anaphylactic-type reactions, are not expected to be present in the formulation product Sivanto 200 SL;
- The end-use product BYI 02960 480 FS, contains the preservative 1,2-benzisothiazoline-3-one which contains low levels of dioxins and furans. These are being managed as outlined in the PMRA Regulatory Directive DIR99-03 for the implementation of TSMP.

## 7.0 Summary

### 7.1 Human Health and Safety

Mixers, loaders and applicators handling flupyradifurone, commercial workers in seed treatment facilities (and mobile treaters), farmers planting and handling treated soybean seeds and workers re-entering treated areas are not expected to be exposed to levels of flupyradifurone that will result in an unacceptable risk when used according to label directions.

---

<sup>6</sup> *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

<sup>7</sup> NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

<sup>8</sup> DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

The personal protective equipment on the product label for workers in commercial seed treatment facilities (and mobile treaters) is coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, goggles, and shoes plus socks. Treater and baggers/sewers/stackers must wear a NIOSH approved respirator. Soybean seeds can only be treated in closed treatment systems. Farmers handling treated seed during planting must wear a long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks. Planters must use a closed cab tractor.

Farmers and custom applicators who mix, load or apply Sivanto 200 SL must wear a long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks.

Bystander exposure is not of concern.

The toxicology database submitted for flupyradifurone is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of carcinogenicity in rats or mice after longer-term dosing. In short- and long-term studies with adult animals, the targets of toxicity were the liver, thyroid gland, kidney, and skeletal muscle. There was no evidence of dysregulation of the immune system. Neurotoxicity was evident after acute gavage dosing, but not after repeated dietary exposures. There was no evidence of increased susceptibility of the young in the rat. In the rabbit, fetal deaths, considered a serious endpoint, were observed in the presence of maternal toxicity. Effects on the reproductive system were noted at a dose higher than that which resulted in systemic toxicity to parental animals. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residue in diverse crops (apple, cotton, rice, tomato, and potato) and animals (goat and hen) is adequately understood. The residue definition in livestock, plants, and rotational crops, for enforcement purposes, is flupyradifurone. The residue definition in livestock, plants and rotational crops for the purpose of dietary exposure assessment is flupyradifurone and DFA, expressed as parent equivalents.

The proposed use of flupyradifurone in/on CG1B, CG1C, CG3-07, CG4-13A, CG4-13B, CG5-13, CG6A, CG6B, CG6C, CG8-09, CG9, CG11-09, CG13-07B, CG13-07F, CG13-07G, CG14-11, CG22B, dry soybeans, sweet corn kernels plus cob with husks removed, field corn, popcorn grain, peanuts, including imported commodities (CG10-Revised, green coffee beans, hops (dried), CG15 (except rice, field corn, popcorn grain and sweet corn kernels plus cob with husks removed), CG20C, prickly pears, and prickly pear pads) does not constitute an unacceptable chronic dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits. The PMRA recommends that the following maximum residue limits be specified for residues of flupyradifurone:



<b>Food Commodity</b>	<b>Recommended MRL (ppm)</b>
<i>Brassica</i> leafy greens (CG4-13B)	40
Leafy greens (CG4-13A)	30
Hops (dried)	10
Leaf petioles vegetables (CG22B)	9.0
<i>Brassica</i> head and stem vegetable group (CG5-13)	6.0
Raisins	5.0
Bushberry (CG13-07B, except highbush cranberries)	4.0
Cereal grains (CG15, except rice, sweet corn kernels plus cob with husks removed, field corn, and popcorn grain), small fruit vine climbing subgroup (CG13-07F, except fuzzy kiwifruit), citrus fruits (CG10 Revised), edible-podded legume vegetables (CG6A), dried shelled pea and bean (CG6C, except soybean), green onions (CG3-07B)	3.0
Succulent shelled garden peas, succulent shelled green peas, succulent shelled English peas, succulent shelled peas, succulent shelled pigeon peas	2.0
Low growing berry (CG13-07G, except lowbush blueberries and cranberries), fruiting vegetables (CG8-09), dry soybeans, green coffee beans	1.5
Root vegetable (CG1B, except sugar beet)	0.9
Undelinted cotton seed (CG20C)	0.8
Pome fruits (CG11-09), prickly pear pads	0.7
Meat byproducts of cattle, goats, horses, and sheep	0.5
Cucurbit vegetables (CG9)	0.4
Prickly pears	0.3
Succulent shelled lima beans, succulent shelled blackeyed peas, succulent shelled cowpeas, succulent shelled southern peas, succulent shelled broad beans	0.2
Meat of cattle, goats, horses, and sheep	0.15
Bulb onions (CG3-07A)	0.09
Fat of cattle, goats, horses, and sheep, milk	0.06
Tuberous and corm vegetables (CG1C), field corn, popcorn grain, sweet corn kernels plus cob with husks removed	0.05
Peanuts	0.04
Tree nuts (CG14-11), meat byproducts of hogs	0.02
Eggs, meat and fat of hogs, fat, meat, meat byproducts of poultry	0.01

## 7.2 Environmental Risk

Flupyradifurone is moderately persistent to persistent in the terrestrial environment and persistent in the aquatic environment with the exception of the photic zones where it is not expected to persist. Flupyradifurone is highly mobile and has a potential to leach to groundwater and enter aquatic environments through surface runoff. Flupyradifurone used as a foliar spray may pose a potential risk to non-target terrestrial and aquatic invertebrates, including bees. When

flupyradifurone is used for soybean seed treatment, it poses a potential risk to birds and small wild mammals. However, no risk to bees is expected through dust-off exposure during planting of treated seeds. The identified risks can be mitigated with spray buffer zones to protect sensitive aquatic habitats from spray drift and through the use of label statements to inform and instruct users regarding potential risks to birds and mammals, bees and beneficial arthropods, and to the environment.

### **7.3 Value**

Flupyradifurone is in a new MoA Subgroup (Subgroup 4D, the Butenolides). MoA Group 4 includes the neonicotoids (Subgroup 4A), nicotine (4B) and sulfoxaflor (4C).

BYI 02960 480 FS protects soybean seedling against soybean aphids and bean leaf beetle adults. Sivanto 200 SL controls aphids, leafhoppers, whiteflies, Colorado potato beetle, scale insects and blueberry maggot and suppresses pear psylla on a variety of outdoor crops. Other MoA Group 4 active ingredients are registered for use on many of these crops and pests. Flupyradifurone is a new MoA for use against aphids and leafhoppers on alfalfa.

### **8.0 Proposed Regulatory Decision**

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Flupyradifurone TC and the end-use products BYI 02960 480 FS and Sivanto 200 SL, containing the technical grade active ingredient flupyradifurone, to protect soybean seedling against soybean aphids and bean leaf beetle adults, and to control aphids, leafhoppers, whiteflies, Colorado potato beetle, scale insects and blueberry maggot and suppresses pear psylla on a variety of outdoor crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

## List of Abbreviations

♀	female
♂	male
$\lambda$	wavelength
$\mu\text{g}$	microgram
$\mu\text{g/kg a.i.}$	microgram per kilogram active ingredient
$\mu\text{m}$	micrometre
$\mu\text{M}$	micromolar
$\mu\text{Pa}$	microPascal
$\tau$	lag time per event
1/n	exponent for the Freundlich isotherm
A	application
a.e.	acid equivalent
a.i.	active ingredient
abs	absolute
a.s.	active substance
ACGIH	American Conference of Governmental Industrial Hygienists
AD	administered dose
ADD	absorbed daily dose
ADI	acceptable daily intake
AFC	antibody forming cell
AGF	aspirated grain fractions
AHETF	Agricultural Handlers Exposure Task Force
ALAT	alanine aminotransferase
ALD	aldrin-epoxidase
ALK	alkaline phosphatase
ALP	alkaline phosphatase
ALS	acetolactate synthase
Appl.	Application
APR	application rate
APTT	activated partial thromboplastin time
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Reentry Task Force
ASAE	American Society of Agricultural Engineers
ASAT	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
AUC	area under the curve
B	blended commodity
BAF	bioaccumulation factor
BBCH	growth development stages for cereals
BCF	bioconcentration factor
BHSE	British Health and Safety Executive
Bq	Becquerel
BROD	benzoxyresorufin



---

BUN	blood urea nitrogen
bw	body weight
BW	generic body weight
bwg	bodyweight gain
6-CNA	6-chloronicotinic acid
CA	California
CAF	composite assessment factor
CalDPR	California Department of Pesticide Regulation
CAS	Chemical Abstracts Service
CCOHS	Canadian Centre for Occupational Health and Safety
CDN	Canadian
CEPA	<i>Canadian Environmental Protection Act</i>
CF	conversion factor
CFIA	Canadian Food Inspection Agency
CFU	colony forming unit
CG	crop group
chol	cholesterol
CI	confidence interval
CK	creatinine kinase
cm	centimetre
C <sub>max</sub>	maximum concentration
CNB	could not be determined
COC	crop oil concentrate
cP	centepoise
CR	chemical resistant
CRC	confined rotational crop
CRD	control rod
CT <sub>50</sub>	clearance time 50% (the time required to observe a 50% decline in concentration in test animal)
CT <sub>90</sub>	clearance time 90% (the time required to observe a 90% decline in concentration in test animal)
Cw	concentration of a.i. in water
d	day(s)
DACO	data code
DA	dermal absorption
DAF	dermal absorption factor
DALA	days after last application
DAT	days after treatment
DEEM	Dietary Exposure Evaluation Model
DER	data evaluation report
DF	dry flowable
DFEAF	difluoroethyl-amino-furanone
DFA	difluoroacetic acid
DFOP	double first-order in parallel
DFR	dislodgeable entry interval
DMA	dimethyl-amine salt
DNA	deoxyribonucleic acid

---

---

DNT	dietary developmental neurotoxicity
DT <sub>50</sub>	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT <sub>75</sub>	dissipation time 75% (the dose required to observe a 75% decline in concentration)
DT <sub>90</sub>	dissipation time 90% (the dose required to observe a 75% decline in concentration)
DU	dust
dw	dry weight
E	total dermal exposure
EbC <sub>50</sub>	EC <sub>50</sub> in terms of algal biomass
EC	emulsion
EC <sub>3</sub>	concentration required to induce a threshold positive sensitization response (SI=3)
EC <sub>05</sub>	effective concentration on 5% of the population
EC <sub>10</sub>	effective concentration on 10% of the population
EC <sub>15</sub>	effective concentration on 15% of the population
EC <sub>25</sub>	effective concentration on 25% of the population
EC <sub>50</sub>	effective concentration on 50% of the population
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ED	exposure duration
EDE	estimated daily exposure
EEC	estimated environmental concentration
EFH	Exposure Factors Handbook
EFSA	European Food Safety Authority
EIIS	USEPA Ecological Incident Information System
EMEA	European Medical Agency
ELS	early life stage
EP	end-use product
EPP	early preplant
ER <sub>25</sub>	effective rate for 25% of the population
ER <sub>50</sub>	effective rate on 50% of the population
ERC	evaluation report
E <sub>r</sub> C <sub>50</sub>	EC <sub>50</sub> in terms of reduction of growth rate
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
ETOT	total erythrocyte cells
EU	European Union
E <sub>y</sub> C <sub>50</sub>	EC <sub>50</sub> in terms of reduction of yield
F	fraction
F <sub>0</sub>	parental generation
F <sub>1</sub>	first generation
F <sub>2</sub>	second generation
FA	fraction of absorbed water
fc	food consumption
fe	food efficiency
F <sub>int</sub>	foliar deposition fraction
FIFRA	US Federal Insecticide, Fungicide and Rodenticide Act

---

---

FIR	food ingestion rate
FL	Florida
FOB	functional observation battery
FPD	Flupyradifurone
FRAC	Fungicide Resistance Action Committee
FS	flowable suspension
F <sub>soil</sub>	soil deposition fraction
Fw	fresh weight
g	gram
g a.i.	grams active ingredient
g a.i./L	grams active ingredient per litre
g/L	grams per litre
G	granular
gal	gallon
GAP	Good Agricultural Practice
GC	gas chromatography
GC-ECD	gas chromatography with electron capture detection
GC-MS	gas chromatography mass spectroscopy
GC-MSD	gas chromatography methods with mass spectrometric detection
GC-NPD	gas chromatography with nitrogen-specific thermionic detection
GD	gestation day
GDH	glutamate dehydrogenase
GGT	gamma glutamyltransferase
GI	gastrointestinal
GIT	gastrointestinal tract
GLP	Good Laboratory Practice
GLU-T	UDP-glucuronyl-transferase
GnRH	gonadotropin-releasing hormone
GPA	gallons per acre
GR	grass residue
GRAS	generally recognized as safe substance
GST	glutathione S-transferase
GUS	groundwater ubiquity score
h	hour(s)
ha	hectare
HAFT	highest average field trial
HC	historical control
HCl	hydrochloric acid
HC <sub>5</sub>	hazardous concentration to 5% of the species
HCT	haematocrit
HDPE	high density polyethylene
HDT	highest dose tested
HED	Health Evaluation Directorate
Hg	mercury
HGB	haemoglobin
HPLC	high performance liquid chromatography

---



---

HPLC-MS/MS	high-performance liquid chromatography with tandem mass spectrometry
hr(s)	hour(s)
HtM	hand-to-mouth
IA	Iowa
IBC	intermediate bulk container
ID	Indiana
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
ILV	independent laboratory validation
IOBC	International Organisation for Biological Control
IORE	indeterminate order rate equation
IPM	integrated pest management
IR-4	Inter-Regional Research Project Number 4
IRAC	Insecticide Resistance Action Committee
IRS	ingestion rate
ISO	International Organization for Standardization
ITS	internally transcribed
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union of Pure and Applied Chemistry
K	Henry's Law Constant
KBr	Potassium Bromide
K <sub>d</sub>	soil-water partition coefficient
K <sub>des</sub>	soil-water desorption coefficient
K <sub>desoc</sub>	soil-water desorption coefficient adjusted according to organic carbon content
K <sub>doc</sub>	soil-water partition coefficient adjusted according to organic carbon content
K <sub>desorb</sub>	soil desorption coefficient
K <sub>F</sub>	Freundlich adsorption coefficient
K <sub>Foc</sub>	Freundlich organic-carbon partition coefficient
kg	kilogram
km	kilometre
K <sub>oc</sub>	organic-carbon partition coefficient
K <sub>ow</sub>	n-octanol-water partition coefficient
K <sub>p</sub>	permeability coefficient
kPa	kiloPascal
L	litre
LADD	lifetime average daily dose
LAFT	lowest average field trial
lb	pound
LC <sub>50</sub>	lethal concentration 50%
LC-MS/MS	liquid chromatography method with tandem mass spectrometry
LD	lactation day
LD <sub>50</sub>	lethal dose 50%
LDH	lactate dehydrogenase
LH	lutinizing hormone

---

---

LHR	luteinizing hormone receptor
LLMV	lowest limit of method validation
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOEC	low observed effect concentration
LOQ	limit of quantitation
LP	late postemergence
LPM	litres per minute
LR <sub>50</sub>	lethal rate 50%
LSC	liquid scintillation counting
m	metre
M/L/A	mixer/loader/applicator
m/z	mass-to-charge ratio of an ion
m <sup>2</sup>	square metre
m <sup>3</sup>	cubic metre
MAS	maximum average score
Max	maximum
MBD	more balanced diet
MBDB	more balanced dietary burden
MCC	maximum challenge concentration
MCH	mean corpuscular hemoglobin
MCHC	mean cell haemoglobin concentration
mCi	millicurie
MCV	mean cell volume
ME	Maine
Met-Hb	methemoglobin
mg	milligram
MI	Michigan
Min	minimum
MIS	maximum irritation score
mL	millilitre
M/L	Mixer/Loader
M/L/A	Mixer/Loader/Applicator
mm	millimetre
mmole	millimole
MoA	mode of action
MOE	margin of exposure
mol	mole
mPa	megaPascal
MPCA	microbial pest control agent
MPN	most probable number
MRID	US Master Record Identification Number
MRL	maximum residue limit
MRM	multiresidue method
MS	mass spectrometry

---

---

MSO	Methylated Seed Oil
MS/MS	tandem mass spectrometry
MTD	maximum tolerated dose
MTOT	total granulopoietic cells
mw	molecular weight
m/z	mass-to-charge ratio for an ion
n	number of field trials
Na	sodium
N/A	not applicable
nAChR	nicotinic acetylcholine receptor
NADPH	nicotinamide adenine dinucleotide phosphate-oxidase
NAFTA	North American Free Trade Agreement
NaOH	sodium hydroxide
NB	Non-blended commodity
NC	North Carolina
ND	North Dakota
Ng	nanogram
NIOSH	National Institute for Occupational Safety and Health
NIS	non-ionic surfactant
NJ	New Jersey
nm	nanometre
NMR	nuclear magnetic resonance
NOAEC	no observed adverse effect concentration
NOAEL	no observable adverse effect level
NOEAER	no observed ecologically adverse effect rate
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
NPD	nitrogen phosphorus detector
N/R	not relevant or not required
NZW	New Zealand white mouse
OB	occlusion bodies
obs	observation
OC	organic carbon content
OCT	ornithine carbamoyl transferase
OCSP	Office of Chemical Safety and Pollution Prevention
OD	oil dispersion
OECD	Organization for Economic Cooperation and Development
OH	Ohio
OM	organic matter content
ON	Ontario
ORETF	Outdoor Residential Exposure Task Force
OtM	object-to-mouth
OVS	OSHA Versatile Sampler
P	parental generation
P450	cytochrome P450 family of enzymes
Pa	Pascal

---



---

PACR	Proposed Acceptability for Continuing Registration document
PB	Partially blended commodity
PBI	plantback interval
PCDD	polychlorinated dibenzodioxin
PCDF	furan
PCNA	proliferating cell nuclear antigen
PCV	packed cell volume
Pcw	steady-state permeability coefficient of the stratum corneum
PD	pyridimidine radiolabel
PDA	photodiode array
PE	late postemergent
PEI	Prince Edward Island
PES	post extraction solids
PF	protection factor from clothing
Pf	processing factor
PFC	plaque-forming cell
pH	measure of the acidity or basicity of an aqueous solution
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pKa	dissociation constant
PLT	platelets
PM	afternoon or evening
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PO	postemergence
ppb	parts per billion
PPE	personal protective equipment
PPI	preplant soil incorporated
ppm	parts per million
PRDD	Proposed Registration Decision Document
PROD	pentoxyresorufin-O-deethylase
PRE	pre-emergence
PRVD	Proposed Re-Evaluation Decision document
PRZM-GW	Pesticide Root Zone Model for GroundWater
PRZM-EXAMS	Pesticide Root Zone Model Exposure Analysis Modeling System
PXR	pregnane X receptor
PYO	pick your own
PZ	pyrazole radiolabel
q <sub>1</sub> *	cancer potency factor
RA	risk assessment
RAC	raw agricultural commodity
RBC	red blood cell count
RD	residue definition
RED	Reregistration Eligibility Decision (USEPA)
REI	restricted entry interval
rel	relative
RQ	risk quotient

---

---

RRD	Re-Evaluation Decision document
RRE	re-arrangement ester
rRNA	ribosomal ribonucleic acid
RSD	relative standard deviation
rT <sub>3</sub>	reverse triiodothyronine hormone
RTI	retreatment interval
SA	surface area
SAC	sacrificed
SC	suspension concentrate
SD	standard deviation
SDHI	Succinate Dehydrogenase Inhibitor
SEF	saliva extraction factor
SEM	scanning electron microscopy
SFO	single first-order
SG	soluble granule
SI	stimulation index
SK	Saskatchewan
SL	soluble liquid concentrate
SN	solution
SOHD	single oral high dose
SOLD	single oral low dose
SOP	standard operating procedure
SPE	solid phase extraction
SPUD	Statistics on Pesticide Use Database
sRBC	sheep red blood cells
SSD	species sensitivity distribution
StAR	steroidogenic acute regulatory protein
STMdR	supervised trial median residue
STMR	supervised trial mean residue
Sulph-Hb	sulphhemoglobin
t	time
t <sub>1/2</sub>	half-life
<i>t<sub>1/2-rep</sub></i>	representative half-life
<i>t<sub>1/2e</sub></i>	elimination half-life
T <sub>3</sub>	tri-iodothyronine
T <sub>4</sub>	thyroxine
tbili	total bilirubin
TC	transfer coefficient
TDAR	T-dependant antigen response
TDE	total dermal exposure
TEM	transmission electron microscopy
TGAI	technical grade active ingredient
TLC	thin layer chromatography
TLV	threshold limit value
T <sub>max</sub>	time to peak blood concentration
TP	transformation product(s)
TRR	total radioactive residue

---

TRT1	untreated control
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
TTR	transferable turf residue
TWA	time weighted average
UAN	urea ammonium nitrate
UDPGT	uridine diphosphate glucuronosyl transferase
UE	unit exposure
UF	uncertainty factor
UK	United Kingdom
US	United States
USC	Use Site Category
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
UTC	untreated control
UV	ultraviolet
v/v	volume per volume dilution
w/v	weight per volume dilution
w/w	weight per weight dilution
WB	water-dispersible briquette
WBC	white blood cells
WDG	water dispersible granule
WG	wettable granule
WHO	World Health Organization
wk	week
WOE	weight-of-evidence
WP	wettable powder
WSSA	Weed Science Society of America
wt	weight
yr	year

## Appendix I Tables and Figures

**Table 1 Residue Analysis**

Matrix	Method ID	Analyte	Method Type	LOQ	Reference	
Soil and sediment	N/A	Flupyradifurone	HPLC-MS/MS	5 ng/g in soil	2239085	
		6-CNA			2239084	
		DFA			2239087	
Water	N/A	Flupyradifurone	HPLC-MS/MS	1.0 ng/mL	2239092	
		BYI 2960-succinamide		5.0 ng/mL	2239093	
		BYI 02960-azabicyclosuccinamide		5.0 ng/mL	2239094	
		DFA		1.0 ng/mL		
Plant matrices Enforcement/Data Gathering (NAFTA)						
Wheat (grain, forage)	RV-001-	BYI 02960	HPLC-MS/MS using internal standards	Expressed in parent	2239053	
Bean/dried bean	P10-02/03	DFEAF		equivalents:	2239069	
Barley (straw)	(01304)	DFA		BYI 02960:	2239071	
Lettuce (head, washings)				0.01 mg/kg ; 0.05 mg/kg (hops)	2239074	
Tomatoes				DFEAF: 0.01 mg/kg	2239075	
Oranges				DFA (wet matrices):	2239392	
Rapeseed				0.02 mg/kg		
Soybean (seed)				DFA (dry matrices):		
Sugar beet (root and tops)				0.05 mg/kg; 0.10 mg/kg (hops)		
Hops (beer, brewer's yeast, draff)						
Hop cones (green and dried)						
Extraction solvents: Acetonitrile:water (4:1; v/v) with 2.2 mL/L formic acid						
Animal matrices-Enforcement/Data Gathering (NAFTA)						
Bovine (muscle, liver, kidney, fat)	RV-004-A11-05	BYI 02960	HPLC-MS/MS using internal standards	Expressed in parent	2239059	
		DFA		equivalents:	2239060	
Poultry (muscle, liver, and fat)		BYI 02960-acetyl-AMCP		BYI 02960:	2239072	
Eggs		BYI 02960-OH		0.01 mg/kg		
Milk/Whole				DFA (poultry tissues):		
Cream/Whey				0.01 mg/kg		
Urine				DFA (bovine tissues):		
Excreta				0.02 mg/kg		
				BYI 02960-acetyl-AMCP: 0.01 mg/kg		
				BYI 02960-OH: 0.01 mg/kg		
Extraction solvents: Acetonitrile:water (4:1; v/v) with 2.2 mL/L formic acid						



**Table 2 Toxicity Profile of End-use Products Containing Flupyradifurone**  
(Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type / Animal / PMRA #	Study Results
<b>End Use Product – SIVANTO 200 SL</b>	
Acute oral (Acute toxic class method) Rat (Wistar) PMRA 2236640	LD <sub>50</sub> > 2000 mg/kg bw Low Toxicity
Acute dermal Rat (Wistar) PMRA 2236649	LD <sub>50</sub> > 2000 mg/kg bw Low Toxicity
Acute inhalation Rat (Wistar) PMRA 2236651	LC <sub>50</sub> (♀) = 4.5 mg/L LC <sub>50</sub> (♂) > 4.5 mg/L Low Toxicity
Dermal irritation Rabbit (NZW) PMRA 2236668	MAS = 0 MIS = 0 Non Irritating
Eye irritation Rabbit (NZW) PMRA 2236678	MAS = 1.8 MIS = 2.7 (at 24 & 48 hours) Minimally Irritating
Dermal sensitization (LLNA) Mouse (CBA/J) PMRA 2236679	SI = 1.3, 2.3 and 3.0 at 25%, 50% and 100% EC <sub>3</sub> = 100% Potential Skin Sensitizer
<b>End Use Product – BYI 02960 480 FS</b>	
Acute oral (Up and down procedure) Rat (Sprague Dawley) PMRA 2236522	LD <sub>50</sub> (♀) = 1030 mg/kg bw Slight Toxicity
Acute dermal Rat (Sprague Dawley) PMRA 2236520	LD <sub>50</sub> > 5000 mg/kg bw Low Toxicity

End Use Product – BYI 02960 480 FS	
Acute inhalation	LC <sub>50</sub> > 5.04 mg/L
Rat (Sprague Dawley)	Low Toxicity
PMRA 2236517	
Dermal irritation	MAS = 0.44 MIS = 1 (at 0.5-1 hour)
Rabbit (NZW)	Minimally Irritating
PMRA 2236516	
Eye irritation	MAS = 0 MIS = 1.67 (at 1 hour)
Rabbit (NZW)	Non Irritating
PMRA 2236514	
Dermal sensitization (LLNA)	SI = 1.05, 1.16, 1.93 at 25%, 50% and 100%
Mouse (CBA/J)	Negative
PMRA 2236513	

**Table 3 Toxicity Profile of Flupyradifurone**

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.)

Study Type / Animal / PMRA #	Study Results
Toxicokinetics  pyridinylmethyl- <sup>14</sup> C furanone-4- <sup>14</sup> C ethyl-1- <sup>14</sup> C  Rat (Wistar)  PMRA 2239258 PMRA 2239417 PMRA 2239502	<p><u>Absorption</u>: Rapid (T<sub>max</sub> ~ 1 hour at low dose, 2-4 hours at high dose) and high (&gt;76% of AD).</p> <p><u>Excretion</u>: Rapid (&gt;98% of AD within 72 hours with the pyridinylmethyl label; &gt;87% of AD within 24 hours with furanone and ethyl labels). Urine was the primary route of excretion (76-91% of AD).</p> <p><u>Distribution</u>: Rapid (residue levels in plasma declined to 50% of C<sub>max</sub> within 4-8 hours at the low dose; and within 8-24 hours at the high dose).</p> <p>The test material was widely distributed, with very low levels (&lt;3% of AD) detected in tissues. The highest levels were detected in blood cells, GIT, and eyes (♀) with the pyridinylmethyl label; in the thyroid, Harderian and adrenal glands with the furanone label; and in plasma and nasal mucosa with the ethyl label.</p> <p><u>Metabolism</u>: Parent compound was predominant in urine (36-74% of AD) and BYI 02960-OH was predominant in feces (2-16% of AD) with all three labels. BYI 02960-OH was prominent in urine (11-14% of AD) with the furanone label. 6-CNA (2-6% of AD) and BYI 02960-hippuric acid (7-10% of AD) were prominent in urine with the pyridinylmethyl label.</p>

	<p>The metabolic profiles were similar for both sexes; ♂ had a higher rate of metabolite formation than ♀.</p> <p>The metabolic reactions for all three labels were (1) hydroxylation followed by conjugation with glucuronic acid or with sulphate, and (2) cleavage of the difluoroethyl group forming BYI 02960-desdifluoroethyl, followed by: (3) cleavage at the pyridinylmethyl bridge forming 6-CNA and glycine conjugation to BYI 02960-hippuric acid for the pyridinylmethyl label; or (3) cleavage at the pyridinylmethyl bridge forming BYI 02960-difluoroethyl-amino-furanone, and (4) cleavage at the nitrogen-carbon bond next to the furanone moiety followed by further conversion to C1 and C2 compounds and degradation to carbon dioxide for the furanone label; or (3) cleavage at the pyridinylmethyl bridge leading to BYI 02960-difluoroethyl-amino-furanone for the ethyl label.</p>
<p>Metabolism in organs and tissues</p> <p>Rat (Wistar)</p> <p>furanone-4-<sup>14</sup>C ethyl-1-<sup>14</sup>C</p> <p>PMRA 2239418 PMRA 2239503</p>	<p><u>Distribution</u>: Highest residue levels were detected in the liver and kidney (both labels), and leg muscle, skin, and fat (ethyl label).</p> <p>With the ethyl label, highest residues in organs/tissues were detected at 1 hour (65/85% of AD in ♂/♀) and residues declined rapidly by 24 hours (&lt;8% of AD).</p> <p><u>Metabolism</u>: The extent of metabolism was greater in ♂ than in ♀.</p> <p>In plasma, organs and tissues, the parent compound was the predominant component (&gt;72% of TRR) for the furanone label, while difluoroacetic acid was predominant (&gt;50% of TRR) for the ethyl label.</p> <p>The principal metabolic reactions were (1) hydroxylation followed by conjugation with glucuronic acid; (2) cleavage of the difluoroethyl group forming BYI 02960-des-difluoroethyl with the furanone label or difluoroacetic acid with the ethyl label; and (3) cleavage of the molecule at the pyridinylmethyl bridge leading to BYI 02960-difluoroethyl-amino-furanone.</p>
<p>Quantitative whole body autoradiography following single oral dose</p> <p>Rat (Wistar)</p> <p>pyridinylmethyl-<sup>14</sup>C furanone-4-<sup>14</sup>C</p> <p>PMRA 2239257 PMRA 2239416</p>	<p><u>Excretion</u>: Urine was the primary route of excretion (81/88-92% of AD in ♂/♀), with 14-22/6-8% (♂/♀) of AD excreted in feces. Less than 3% of AD was detected in expired air within 48 hours.</p> <p><u>Distribution</u>: Maximum residue levels were detected in almost all organs and tissues at 1 hour, with highest levels in the liver, kidney and hormonal/secretory glands (thyroid, adrenal, Harderian, salivary glands) for both labels, and in the brown fat, myocardium, and olfactory bulb for the furanone label.</p> <p>For the pyridinylmethyl label, residue levels declined to &lt;5% of the maximum for most organs and tissues within 24 hours, and to &lt;LOQ within 168 hours.</p> <p>For the furanone label, comparatively high levels were detected in the nasal mucosa at 168 hours.</p> <p>Residues from organs and tissues declined from peak values with biphasic kinetics. The results support the biotransformation of the furanone ring into small carbon fragment and subsequent formation of <sup>14</sup>CO<sub>2</sub> and incorporation into the carbon pool of endogenous compounds.</p>
<p>Acute oral (Acute toxic class method)</p> <p>Rat (Wistar)</p> <p>PMRA 2239256</p>	<p>LD<sub>50</sub> = 300-2000 mg/kg bw</p> <p>Slight Toxicity</p>

Acute dermal Rat (Wistar) PMRA 2239415	LD <sub>50</sub> > 2000 mg/kg bw  Low Toxicity
Acute inhalation Rat (Wistar) PMRA 2239500	LC <sub>50</sub> > 4.671 mg/L  Low Toxicity
Dermal irritation Rabbit (NZW) PMRA 2239523	MAS = 0 MIS = 0  Non Irritating
Eye irritation Rabbit (NZW) PMRA 2239543	MAS = 1.1 MIS = 4.7 (1 hour)  Minimally Irritating
28-day dermal Rat (Wistar) PMRA 2239546	NOAEL = 500 mg/kg bw/day LOAEL not established as no adverse effects were observed up to the highest dose tested.
90-day inhalation Waiver rationale PMRA 2284001	Waiver request granted for current submission only based on low volatility and margins of exposure.
28-day oral (dietary) Mouse (C57BL/6J) PMRA 2239302	NOAEL (♂) = 78 mg/kg bw/day NOAEL (♀) = 192 mg/kg bw/day LOAEL (♂) = 166 mg/kg bw/day, based on bw loss week 1, ↓ bwg. LOAEL (♀) not established as no adverse effects were observed up to the highest dose tested.
90-day oral (dietary) Mouse (C57BL/6J) PMRA 2239436	NOAEL = 81/98 mg/kg bw/day in ♂/♀ LOAEL = 407/473 mg/kg bw/day in ♂/♀, based on ↓ fc, ↓ cholesterol, ↓ protein, ↑ BUN, ↑ ALK, ↑ ALAT, ↑ ASAT, ↑ severity of hepatocellular hypertrophy; ↓ bw, ↓ bwg, ↓ kidney wt, loss of normal cortical epithelial vacuolation in kidney (♂); ↓ albumin, ↑ liver weight, pale liver (♀).  Plasma concentrations of parent compound increased linearly with dose, and were slightly higher in males than in females at all doses (1.2 to 1.6-fold).
28-day oral (gavage) Rat (Wistar) PMRA 2239332	NOAEL = 75 mg/kg bw/day in ♂&♀ LOAEL = 200 mg/kg bw/day in ♂&♀, based on salivation (starting at day 2), ↓ bilirubin, ↑ liver wt, hepatocellular hypertrophy; ↓ glucose, ↑ BROD, ↓ spleen wt, lobulation of liver, enlarged liver, thyroid follicular cell hypertrophy (♂); 1 death day 2, ↓ fc week 1, ↑ triglycerides, ↑ creatinine, ↑ ALAT (♀).
28-day oral (dietary) Rat (Wistar) PMRA 2239311	NOAEL = 34 mg/kg bw/day in ♂ (♀ not tested in this study) LOAEL = 385 mg/kg bw/day in ♂, based on ↓ bw, ↓ bwg, ↓ fc, ↓ glucose, ↓ bilirubin, ↑ BUN, ↑ cholesterol, ↑ TSH, ↓ T4, ↑ BROD, ↑ UDPGT, ↑ liver wt, ↑ thyroid wt, lobulation of liver, hepatocellular hypertrophy, thyroid follicular cell hypertrophy.



90-day oral (dietary) Rat (Wistar) PMRA 2239420	<p>NOAEL = 30/38 mg/kg bw/day in ♂/♀ LOAEL = 156/186 mg/kg bw/day in ♂/♀, based on ↓ bw, ↓ bwg, ↓ fc, ↓ bilirubin, ↓ glucose, ↑ cholesterol, ↑ triglycerides, ↑ liver wt, ↑ thyroid wt, enlarged liver, hepatocellular hypertrophy; prominent lobulation of liver, dark colored thyroid, thyroid follicular cell hypertrophy (♂); ↑ platelets, ↑ WBC (♀).</p> <p>Plasma concentrations of parent compound increased in a linear fashion between 100 and 500 ppm (5-fold) but in a sub-linear fashion between 100 and 2500 ppm (15-21-fold). Plasma concentrations of parent were slightly higher in females than in males at all dose levels (1.3 to 1.7-fold).</p>
28-day oral (dietary) Dog (Beagle) PMRA 2239321	<p>NOAEL/LOAEL not established due to small group sizes (2/sex/dose)</p> <p>Effects at 62/77 mg/kg bw/day in ♂/♀ included ↓ bwg, ↓ fc, ↓ hepatic centrilobular glycogen accumulation (♂); ↑ platelets (♀).</p>
90-day oral (dietary) Dog (Beagle) PMRA 2239504	<p>NOAEL = 12 mg/kg bw/day in ♂/♀ LOAEL = 33/41 mg/kg bw/day in ♂/♀, based on ↓ bw, ↓ bwg, ↓ fc, ↑ CK, ↑ ASAT, ↑ ALAT, minimal to slight skeletal muscle myofiber atrophy/degeneration; ↑ rel. kidney wt (♂).</p> <p>At the next higher dose of 102/107 mg/kg bw/day in ♂/♀, unsteady and stiff back legs and lower back were observed (1/sex).</p>
1-year oral (dietary) Dog (Beagle) PMRA 2239521	<p>NOAEL = 7.8 mg/kg bw/day in ♂ &amp; ♀ LOAEL = 28 mg/kg bw/day in ♂ &amp; ♀, based on minimal to slight skeletal muscle myofiber degeneration; ↓ bw, ↓ bwg (♀).</p> <p>Plasma levels of parent compound peaked at 3 hours after withdrawal of food; levels in males were 1.3-1.5-fold higher than levels in females.</p>
18-month oncogenicity (dietary) Mouse (C57BL/6J) PMRA 2239506	<p>NOAEL = 43/53 mg/kg bw/day in ♂/♀ LOAEL = 224/263 mg/kg bw/day in ♂/♀, based on ↓ bw, ↓ bwg; ↓ kidney wt, ↑ liver wt, ↑ platelets, atrophic/small kidney, ↓ incidence of bilateral basophilic tubules, ↓ incidence of focal renal cortical mineralization and corticocapillary vacuolation, ↑ incidence and severity of diffuse hepatocellular vacuolation (♂); ↑ rel. liver wt, ↓ incidence of diffuse hepatocellular macrovacuolation (♀).</p> <p>Plasma levels of parent compound followed linear increasing trend with dose. Levels in males were slightly higher than those in females (1.1 to 1.7-fold). Levels at week 52 were comparable to those at week 78.</p> <p>No evidence of oncogenicity</p>
2-year combined chronic toxicity/oncogenicity (dietary) Rat (Wistar) PMRA 2239460	<p>NOAEL = 16/22 mg/kg bw/day in ♂/♀ LOAEL = 81/120 mg/kg bw/day in ♂/♀, based on ↓ bw, ↓ bwg, ↑ WBC, ↓ bilirubin, ↑ rel. liver wt, hepatocellular hypertrophy, hepatocellular macrovacuolation, colloid alteration of the thyroid gland, thyroid follicular cell hypertrophy; soiled fur, alopecia, hyper-reactivity to external stimuli, resistance to handling, enlarged/pale liver, foci of hepatocellular alteration (♂); soiled fur, alopecia, ↓ fc, lens opacity, ↑ platelets, ↑ cholesterol, non-adverse hematology findings (↓ MCV, ↓ MCH, ↓ HGB, ↓ HCT), hepatocellular brown pigment, interstitial mononuclear cell infiltrate of liver, accumulation of brown pigment in Kupffer cells, brown pigmentation of thyroid follicular cells, white foci in lung, alveolar foamy macrophages, chronic interstitial &amp; perivascular inflammation of lung (♀).</p> <p>Plasma concentrations of parent compound increased with dose in a nearly linear fashion for females but in a sub-linear fashion for males. Plasma concentrations of</p>

	<p>parent were slightly higher in females than in males at 400 and 2000 ppm (1.1 to 1.8-fold). Levels at week 52 were comparable to those at week 104.</p> <p>No evidence of oncogenicity</p>
<p>2-generation reproduction (dietary)</p> <p>Rat (Wistar)</p> <p>PMRA 2239237</p>	<p>Parental NOAEL = 32/39 mg/kg bw/day in ♂/♀</p> <p>Parental LOAEL = 120/140 mg/kg bw/day in ♂/♀, based on ↑ liver wt (P), ↑ abs. thyroid wt (P), ↑ rel. thyroid wt (P&amp;F<sub>1</sub>), hepatocellular hypertrophy (P) (♂); ↓ fc pre-mating (P&amp;F<sub>1</sub>), ↓ bw pre-mating (P), ↓ bwg pre-mating (P), ↑ bwg lactation (P&amp;F<sub>1</sub>) (♀).</p> <p>Offspring NOAEL = 7.8 mg/kg bw/day</p> <p>Offspring LOAEL = 39 mg/kg bw/day, based on ↓ bw LD 14-21 (F<sub>2</sub>), ↓ bwg F<sub>2</sub>.</p> <p>Reproductive NOAEL = 32/39 mg/kg bw/day in ♂/♀</p> <p>Reproductive LOAEL = 120/140 mg/kg bw/day in ♂/♀, based on ↓ epididymal sperm count (P<sub>1</sub>&amp;F<sub>1</sub> adults), ↓ testicular sperm count (P<sub>1</sub> adults), ↓ number of estrous cycles (F<sub>1</sub> adults), ↓ implantations (F<sub>1</sub> adults), ↓ number of pups born (F<sub>2</sub> pups), ↓ mean litter size (F<sub>2</sub> pups).</p> <p>Evidence of sensitivity of the young</p>
<p>Developmental toxicity (gavage)</p> <p>Rat (Sprague Dawley)</p> <p>PMRA 2239547</p>	<p>Maternal NOAEL = 50 mg/kg bw/day</p> <p>Maternal LOAEL = 150 mg/kg bw/day, based on salivation, bw loss GD 6-8, ↓ bwg GD 8-10, ↓ corrected bwg, ↓ fc GD 6-12.</p> <p>Developmental NOAEL = 50 mg/kg bw/day</p> <p>Developmental LOAEL = 150 mg/kg bw/day, based on incomplete ossification of parietal and hyoid centra.</p> <p>No evidence of sensitivity of the young</p>
<p>Developmental toxicity (gavage) – Dose range-finding study and main study</p> <p>Rabbit (NZW)</p> <p>PMRA 2351717</p> <p>PMRA 2239577</p>	<p>NOAEL/LOAEL were established based on combined data from the main study and the dose range-finding study.</p> <p>Maternal NOAEL = 40 mg/kg bw/day</p> <p>Maternal LOAEL = 80 mg/kg bw/day, based on no or few feces, bw loss GD 6-8, ↓ corrected bwg, ↓ fc GD 6-10.</p> <p>Developmental NOAEL = 40 mg/kg bw/day</p> <p>Developmental LOAEL = 80 mg/kg bw/day, based on ↑ dead fetuses, ↓ fetal bw.</p> <p>Serious endpoint in the young (fetal deaths) in the presence of maternal toxicity.</p>
<p>Acute oral neurotoxicity (gavage)</p> <p>Rat (Wistar)</p> <p>PMRA 2239240</p>	<p>NOAEL = 35 mg/kg bw in ♂&amp;♀</p> <p>LOAEL = 50 mg/kg bw in ♂&amp;♀, based on piloerection; pupil dilation (♀).</p> <p>Effects noted at the next higher dose of 200 mg/kg bw in ♂&amp;♀ included flaccid muscle tone, clonic tremors, gait incoordination, rapid respiration, low arousal, flattened or hunched posture, repetitive licking of lips, ↓ rearing, exaggerated flexor reflexes, ↓ motor activity first 10 minutes of testing; cold to touch, myoclonic jerks, absence of movement, pupil dilation (♂); walking on tiptoes (♀).</p> <p>All FOB findings were observed on the day of dosing</p>
<p>90-day oral neurotoxicity (dietary)</p> <p>Rat (Wistar)</p>	<p>NOAEL = 29/35 mg/kg bw/day in ♂/♀</p> <p>LOAEL = 143/173 mg/kg bw/day in ♂/♀, based on ↓ bw, ↓ bwg, ↓ fc week 1; enlarged liver (♀).</p>

PMRA 2239524	
Developmental neurotoxicity (dietary)	Maternal NOAEL = 42 mg/kg bw/day Maternal LOAEL = 102 mg/kg bw/day, based on ↓ bw, bwg, fc during gestation.
Rat (Wistar)	Offspring NOAEL = 42 mg/kg bw/day
PMRA 2239537	Offspring LOAEL = 102 mg/kg bw/day, based on ↓ bw PND 17 & 21, ↓ bwg PND 4-21; ↑ motor and locomotor activity PND 13 (♂); ↑ auditory startle amplitude PND 60 (♀).
	No evidence of sensitivity of the young.
28-day immunotoxicity (dietary)	NOAEL = 50 mg/kg bw/day in ♀ (♂ were not tested in this study) LOAEL = 230 mg/kg bw/day in ♀, based on ↓ bw, ↓ bwg, ↓ fc.
Rat (Wistar)	
PMRA 2239155	
Bacterial reverse mutation	Negative
<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, TA1537	
PMRA 2239254	
Bacterial reverse mutation	Negative
<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, TA1537	
PMRA 2239255	
In vitro forward mutation assay in mammalian cells	Negative
Chinese hamster V79 lung cells	
PMRA 2239505	
In vitro chromosomal aberration assay	Negative
Chinese hamster V79 lung cells	
PMRA 2239414	
In vivo micronucleus assay	Negative
Mouse (NMRI)	
PMRA 2239535	

In vivo micronucleus assay	Negative
Mouse (NMRI)	
PMRA 2239536	
Plasma biokinetics after 7 days of dietary administration	C <sub>max</sub> measured at 8 a.m. in ♂; 2 p.m. in ♀.
PMRA 2239156	<p>Considering inter-individual variability, plasma concentrations of parent compound were similar at all three times periods for both sexes (range of 7.8-8.3 mg/L in ♂, 8.8-9.4 mg/L in ♀).</p> <p>Blood samples collected between 8 a.m. and 5 p.m. are adequate for measuring parent compound in plasma around the C<sub>max</sub> for both sexes, which correspond to a T<sub>max</sub> at between 6 hours and 15 hours after the beginning of the dark period.</p> <p>In long-term studies with dark period from 7 p.m. to 7 a.m., assuming animals start eating food at beginning of dark period, the blood collection can be performed between 1 a.m. and 10 a.m. to measure the parent compound.</p>

**Table 4 Toxicity Profile of Flupyradifurone Metabolites**

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.)

Study Type / Animal / PMRA #	Study Results
<b>Metabolite (6-chloro-3-pyridyl) methanol</b>	
Acute oral	LD <sub>50</sub> (♂) = 1842 mg/kg bw
Rat (Sprague Dawley)	LD <sub>50</sub> (♀) = 1483 mg/kg bw
PMRA 2239146	Slight Toxicity
90-day oral (dietary)	NOAEL (♂) = 49 mg/kg bw/day
Rat (Sprague Dawley)	NOAEL (♀) = 276 mg/kg bw/day
PMRA 2239147	<p>LOAEL (♂) = 250 mg/kg bw/day, based on eosinophilic intranuclear inclusions in proximal tubular epithelium of kidney.</p> <p>LOAEL (♀) = 1174 mg/kg bw/day, based on ↓ bw, ↓ bwg, ↓ fc, ↓ food efficiency week 1, ↓ glucose; ↑ ALK, eosinophilic intranuclear inclusions in proximal tubular epithelium of kidney (♀).</p>
Bacterial reverse mutation	Negative
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. Coli</i> WP2 uvrA	
PMRA 2239148	



Study Type / Animal / PMRA #	Study Results
<b>Metabolite 6-chloronicotinic acid</b>	
Acute oral  Rat (Sprague Dawley)  PMRA 2239149	LD <sub>50</sub> > 5000 mg/kg bw  Low Toxicity
Bacterial reverse mutation  <i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. Coli</i> WP2 uvrA  PMRA 2239150	Negative

<b>Metabolite difluoroacetic acid</b>	
Acute oral (Acute toxic class method)  Rat (Sprague Dawley)  PMRA 2239132	LD <sub>50</sub> = 300-2000 mg/kg bw  Slight Toxicity
90-day oral (dietary)  Rat (Wistar)  PMRA 2239105	NOAEL = 13/16 mg/kg bw/day in ♂/♀ LOAEL = 66/79 mg/kg bw/day in ♂/♀, based on ↓ bw, ↓ bwg, ↓ fc, ↓ glucose, ↓ bilirubin, ↓ WBC, ↑ urinary volume, ↑ urinary ketones, black foci in glandular stomach (1-3 rats), erosion/necrosis of glandular stomach (1-2 rats).
Bacterial reverse mutation  <i>S. typhimurium</i> TA98, TA100, TA102, TA1535, TA1537  PMRA 2239122	Negative
In vitro forward mutation assay in mammalian cells  Chinese hamster V79 lung cells  PMRA 2239126	Negative

In vitro chromosomal aberration assay	Negative
Chinese hamster V79 lung cells	
PMRA 2239123	

Metabolite BYI 02960-difluoroethyl-amino-furanone	
Acute oral (Acute toxic class method)	LD <sub>50</sub> > 2000 mg/kg bw
Rat (Sprague Dawley)	Low Toxicity
PMRA 2239133	
28-day oral (dietary)	NOAEL = 244/273 mg/kg bw/day
Rat (Wistar)	LOAEL not established as no adverse effects were noted up to the highest dose tested.
PMRA 2239154	
Bacterial reverse mutation	Negative
<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, TA1537	
PMRA 2239128	
In vitro forward mutation assay in mammalian cells	Negative
Chinese hamster V79 lung cells	
PMRA 2239130	
In vitro chromosomal aberration assay	Positive
Chinese hamster V79 lung cells	Increased frequency of aberrant cells (with and without gaps) in the absence of metabolic activation.
PMRA 2239131	
In vivo micronucleus assay	Negative
Mouse (NMRI)	
PMRA 2239152	

In vivo unscheduled DNA synthesis	Negative
Rat (Wistar)	
PMRA 2239153	

**Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Flupyradifurone**

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or Target MOE <sup>1</sup>
Acute dietary – general population	Acute oral neurotoxicity study in the rat	NOAEL = 35 mg/kg bw Piloerection, dilated pupils	100
	ARfD (general population) = 0.35 mg/kg bw		
Acute dietary – females 13-49 years of age	Oral developmental toxicity studies in the rabbit	Developmental NOAEL = 40 mg/kg bw, based on increased fetal deaths and reduced fetal body weight, observed in the presence of maternal body weight loss/decreased body weight gain	300 <sup>2</sup>
	ARfD (females 13-49 years) = 0.13 mg/kg bw		
Chronic dietary	Two co-critical studies:  Two-generation dietary reproductive toxicity study in the rat  One-year dietary study in the dog	NOAEL = 7.8 mg/kg bw/day  Offspring NOAEL = 7.8 mg/kg bw/day in two-generation reproductive toxicity study in rats, based on reduced offspring body weights  NOAEL = 7.8 mg/kg bw/day in the on-year dietary study in the dog, based on reduced body weight and skeletal muscle myofiber degeneration	100
	ADI = 0.08 mg/kg bw/day		
Short-term, intermediate-term, & long-term dermal <sup>3</sup> and inhalation <sup>4</sup>	Two co-critical studies:  Two-generation dietary reproductive toxicity study in the rat  One-year dietary study in the dog	NOAEL = 7.8 mg/kg bw/day  Offspring NOAEL = 7.8 mg/kg bw/day in two-generation reproductive toxicity study in rats, based on reduced offspring body weights  NOAEL = 7.8 mg/kg bw/day in the on-year dietary study in the dog, based on reduced body weight and skeletal muscle myofiber degeneration	100
Cancer	A cancer risk assessment was not required		

<sup>1</sup> CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments.

<sup>2</sup> Includes a 3-fold *Pest Control Products Act* factor to account for a serious endpoint (fetal death) observed in the presence of maternal toxicity.

<sup>3</sup> Since an oral NOAEL was selected, a dermal absorption factor was used in a route-to-route extrapolation.

<sup>4</sup> Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

**Table 6 Exposure & risk estimates for workers in commercial seed treatment facilities treating soybeans with BYI 02960 480 FS**

Scenario	kg a.i. handled per day	Unit Exposure (µg/kg a.i. handled)		Exposure <sup>1,2</sup> (mg/kg bw/day)		Combined MOE <sup>3</sup>
		Dermal	Inhalation	Dermal	Inhalation	
Treater/Applicator	28.3	53.5	4.33	$5.31 \times 10^{-3}$	$1.53 \times 10^{-3}$	1140
Bagger/Sewer/Stacker	28.3	115.5	8.9	$3.68 \times 10^{-3}$	$3.15 \times 10^{-3}$	1140
Cleanout Personnel	45 g a.i./100 kg seed	56.2 µg/g a.i./100 kg seed/day	20 µg/g a.i./100 kg seed/day	$2.85 \times 10^{-3}$	$1.13 \times 10^{-2}$	553

<sup>1</sup> For treaters/applicators and baggers/sewers/stackers:

$$\text{Exposure (mg/kg bw/day)} = \frac{\text{Unit exposure (µg/kg a.i. handled per day)} \times \text{kg a.i. handled per day} \times \text{DA (28\% or 9\%)}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$$

<sup>2</sup> For Cleanout personnel, unit exposures are normalized for application rate (the highest application rate proposed was used) therefore:

$$\text{Exposure (mg/kg bw/day)} = \frac{\text{Unit exposure (µg/g a.i./100 kg seed/day)} \times \text{application rate (g a.i./100 kg seed)}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$$

<sup>3</sup> Combined MOE = NOAEL (7.8 mg/kg bw/day) ÷ [Dermal Exposure (mg/kg bw/day) + Inhalation Exposure (mg/kg bw/day)], target MOE= 100

**Table 7 Mixer/loader/applicator exposure and risk to flupyradifurone from Sivanto 200 SL**

Application Method	Maximum Single Application Rate (kg a.i./ha)	ATPD (ha/day) <sup>1</sup>	Dermal Unit Exposure Value (µg/kg ai handled) <sup>3</sup>	Dermal Exposure (mg/kg bw/day) <sup>4</sup>	Inhalation Unit Exposure Value (µg/kg ai handled) <sup>5</sup>	Inhalation Exposure (mg/kg bw/day) <sup>4</sup>	Combined MOE <sup>6</sup>
Foliar Application							
Groundboom (Liquid M/L/A)	0.2	360	84.12	0.02120	2.56	0.002304	332
Aerial (Liquid M/L (open))		400	32.77	0.009176	1.6	0.0016	724
Aerial (Liquid Application)		400	9.66	0.002705	0.07	0.00007	2810
Airblast (Liquid M/L/A)		20	3820.14	0.05348	10.68	0.000534	144
Backpack (M/L/A)		150 L/day	5445.85	0.005718	62.1	0.0002329	1310
Soil Application							
Soil Injection (M/L)	0.4	26	51.14	0.001861	1.6	0.000208	3770
Chemigation (M/L)		40 <sup>2</sup>	51.14	0.002864	1.6	0.000318	2450

<sup>1</sup> Area treated per day values are derived from PMRA default values except for chemigation and soil injection which came from PMRA and the applicant.

<sup>2</sup> 40 ha per day is from applicant data under DACO 5.3

<sup>3</sup> Dermal unit exposure values were taken from PHED (2002) for a single layer with gloves, liquid open pour and open cab.



Groundboom PHED value does not include gloves. Aerial M/L takes into account DIR 96-04 and the unit exposure value is for a double layer with gloves. Aerial application unit exposure value is from a single layer without gloves. Airblast applicator dermal and inhalation unit exposure values are taken from an AHETF study summarized in the January 29<sup>th</sup>, 2014 memo "Revised Unit Exposure Values for Open Cab Airblast Applicators". The M/L exposure of the airblast scenario is derived from PHED.

<sup>4</sup> Dermal/Inhalation Exposure (mg/kg bw/day) = Maximum Application Rate (kg a.i./ha) × ATPD (ha/day) × Dermal/Inhalation Unit Exposure (µg/kg a.i. handled) × Absorption Value (if applicable) ÷ Body Weight (80 kg) × Conversion Factor (1000 µg/mg). For backpack, the ATPD of 150L/day was divided by the spray volume (100 L/ha) in order to multiply by the application rate.

<sup>5</sup> Inhalation unit exposure values from PHED (2002) are light except for backpack which is moderate. The AHETF for airblast inhalation is also light.

<sup>6</sup> Combined MOE = NOAEL (7.8 mg/kg bw/day) ÷ [Dermal Exposure (mg/kg bw/day) + Inhalation Exposure (mg/kg bw/day)], Target MOE = 100

**Table 8 Exposure & risk estimates from planting soybeans seeds treated commercially with BYI 02960 480 FS**

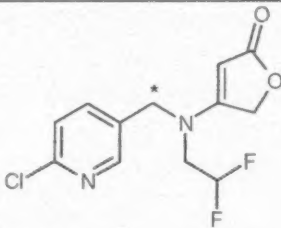
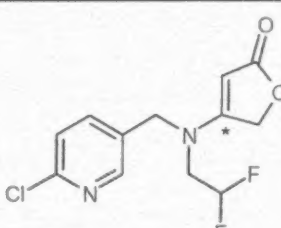
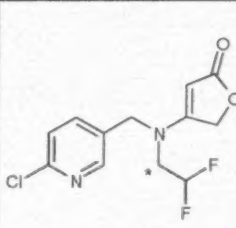
kg a.i. handled per day <sup>1</sup>	Unit Exposure (µg/kg a.i. handled)		Exposure <sup>2</sup> (mg/kg bw/day)		Combined MOE <sup>3</sup>
	Dermal	Inhalation	Dermal	Inhalation	
4.1	1515	82.83	$7.00 \times 10^{-3}$	$4.25 \times 10^{-3}$	694

<sup>1</sup> Estimated amount (kg) a.i. handled per day by a planter = 100 ha/day × 90 kg seed/ha × 45 g a.i./100 kg seed × Conversion Factor (kg/1000g) = 4.1 kg a.i./day

<sup>2</sup> Exposure (mg/kg bw/day) = Unit exposure (µg/kg a.i. handled per day) × kg a.i. handled per day × DA (9%)  
80 kg bw × 1000 µg/mg

<sup>3</sup> Combined MOE = NOAEL (7.8 mg/kg bw/day) ÷ [Dermal Exposure (mg/kg bw/day) + Inhalation Exposure (mg/kg bw/day)], target MOE = 100

**Table 9 Integrated Food Residue Chemistry Summary**

NATURE OF THE RESIDUE STUDIES		
The nature of the residue of flupyradifurone was investigated in primary crops (apple, cotton, rice, tomato, and potato) using different application techniques (foliar, soil drench, granular, and seed piece/in-furrow), and in confined rotational crops (wheat, Swiss chard, and turnips). During the investigation of the environmental fate of flupyradifurone (BYI 02960), difluoroacetic acid (DFA) was found to be a major <u>soil</u> metabolite. Since this metabolite could not be detected by radioactivity in the primary and secondary plant metabolism studies with [furanone-4- <sup>14</sup> C]-BYI 02960 and [pyridinylmethyl- <sup>14</sup> C]-BYI 02960, all sample materials from the nature of the residue studies were analysed for DFA by LC-MS/MS according to residue analytical method 01304.		
Positions of the Radiolabels		
		
[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960	[Furanone-4- <sup>14</sup> C]-BYI 02960	[Ethyl-1- <sup>14</sup> C]-BYI 02960 (Tomato only)

Treatment Type	Fruiting Crops	Root/Tuber Crops	Pulses and Oilseeds	Cereals (Rice)
Foliar Treatment [Sivanto 200 SL]	<u>Apple</u> 1) 1 foliar treatment 2) 2 foliar treatments	NA	<u>Cotton</u> 1) 1 foliar treatment 2) 2 foliar treatments	<u>Paddy Rice</u> 1) 2 foliar treatments
Soil Treatment [Sivanto 200 SL] Seed Treatment [480 FS]	<u>Tomato</u> 1) Soil drench	<u>Potato</u> 1) Potato seed piece treatment 2) In-furrow spray at planting	NA	<u>Paddy Rice</u> 2) Granular at transplanting
Analytical Method Overall TRR Identification & Characterization		Combustion/Liquid Scintillation Counting (LSC)		
Difluoroacetic acid (DFA)		LC-MS/MS		
Extraction Solvents		LC-MS/MS residue method 01304 (non-radiolabelled DFA)		
Post-Extraction Solids (PES)		Acetonitrile: Water (8:2, v/v)		
		Microwave Assisted Extraction (60°C and 120°C)		
		Additional NaCl/diastase digestion step (rice)		
		Additional cellulase digestion step (apples)		
Storage Interval (harvest to analysis) ≤18°C		Apples: Fruit (2.0-2.5 months); Leaves (4 months) Cotton: Cottonseeds (1.6-2.1 months); Lint (0.7 month); Gin trash (0.5 month) Potatoes: Tubers (2.6-3.0 months) Tomatoes: Fruits (1.0-1.5 months); Leaves (3.0 months); Flowers (1.5 months) Paddy Rice: Kernels (2 months); Husks (3.2-3.5); Straw (1.7-1.9 months)		

Nature of the Residue in Tomatoes				PMRA No. 2239378, 2239379, 2239380			
Crop/Variety	Radiolabel	Formulated Product	Type of Treatment	Application Details			
				Growth Stage at Application	Rate (g ai/ha)	# of appl.	PHI (days)
Tomato fruit/ <i>Philona</i>	[Ethyl-1- <sup>14</sup> C]-BYI 02960 35.46µCi/mg; >99% purity	SL 200	Soil drench	1. BBCH 14-15 2. BBCH 51-59 14-d interval	300 Total: 600	2	56
	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960 39.36µCi/mg; >99% purity	SL 200	Soil drench	1. BBCH 14-15 2. BBCH 51 14-d interval	300 Total: 600	2	73
	[Furanone-4- <sup>14</sup> C]-BYI 02960 35.50µCi/mg; >99% purity	SL 200	Soil drench	1. BBCH 14-15 2. BBCH 51 14-d interval	300 Total: 600	2	69
Soil Type		Einheitserde T (white moor peat and clay soil); pH of 5.8					
Testing Environment		Greenhouse					
Overall TRR in Tomato Matrices							
Treatment Type		2 drench applications; PHI = 56-73 days					
Radiolabel Position		[Furanone-4- <sup>14</sup> C]	[Pyridinylmethyl- <sup>14</sup> C]	[Ethyl-1- <sup>14</sup> C]			
Tomato Fruits TRR (ppm)		0.096	0.130	0.201			
Tomato Flowers TRR (ppm)		0.721	1.254	2.230			
Predominant Residues in/on Tomato Fruits and Flowers (≥10% of the TRR) Expressed as Parent Equivalents							

Radiolabels	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960; [Furanone-4- <sup>14</sup> C]-BYI 02960; [Ethyl-1- <sup>14</sup> C]-BYI 02960			
Crop	Tomato Fruits		Tomato Flowers	
Analytes	% TRR	(ppm)	% TRR	(ppm)
Parent	10.0-35.9	0.020-0.034	33.0-77.9	0.561-0.829
DFA	86.6	0.175	59.8	1.334
Glucose/CHO	27.5	0.026	--	--
BYI 02960-6-CNA	13.2	0.017	--	--

BYI 02960-CHMP-di-glyc		37.1	0.048	--	--		
Difluoroethyl-amino-furanone		10.3	0.010	--	--		
Nature of the Residue in Potato Tubers				PMRA No. 2239371, 2239372			
Crop/Variety	Radiolabel	Formulated Product	Type of Treatment	Application Details			
				Growth Stage at Application	Rate (g ai/ha)	# of appl.	PHI (days)
Potato tubers/ <i>Cilena</i>	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960 118.08µCi/mg; >99% purity	FS 480	Seed piece at planting	BBCH 03	254	1	97
	[Furanone-4- <sup>14</sup> C]-BYI 02960 106.46µCi/mg; >99% purity	FS 480	Seed piece at planting	BBCH 03	254	1	97
	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960 118.08µCi/mg; >99% purity	SL 200	In-furrow soil	BBCH 03	625	1	97
	[Furanone-4- <sup>14</sup> C]-BYI 02960 106.46µCi/mg; >99% purity	SL 200	In-furrow soil	BBCH 03	625	1	97
Soil Type		Monheim 4 (sandy loam); pH of 6.8					
Testing Environment		Glass-roofed vegetation area					

<b>Overall TRR in Potato Matrices</b>				
Treatment Type	Seed Piece Treatment; PHI = 97 days		In-Furrow Treatment; PHI = 97 days	
Radiolabel position	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960	[Furanone-4- <sup>14</sup> C]-BYI 02960	Pyridinylmethyl- <sup>14</sup> C]-BYI 02960	[Furanone-4- <sup>14</sup> C]-BYI 02960
Matrices	TRR (ppm)	TRR (ppm)	TRR (ppm)	TRR (ppm)
Potato tubers	0.076	0.078	0.115	0.171
Potato leaves and roots	8.40	6.97	12.44	7.01
Remainders of potato seed pieces	33.33	36.21	6.91	3.43
<b>Predominant Residues in/on Potato Tubers (≥10% of the TRR) Expressed as Parent Equivalents</b>				
Radiolabels	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960; [Furanone-4- <sup>14</sup> C]-BYI 02960			
Crop/Treatment Type	Potato/Seed Piece Treatment		Potato/In-Furrow Treatment	
Analytes	% TRR	(ppm)	% TRR	(ppm)
Parent	40.0-40.2	0.031	44.1-56.8	0.051-0.097
BYI 02960-6-CNA	21.5	0.016	18.4	0.021
DFA (as parent equivalents)*	0.40		0.55	

\*ppm equivalents = 289/95 × residue level of DFA

<b>Nature of the Residue in Apples</b>				<b>PMRA No. 2239375, 2239393</b>			
Crop/Variety	Radiolabel	Formulated Product	Type of Treatment	Application Details			
				Growth Stage at Application	Rate (g ai/ha)	# of appl.	PHI (days)
Apples/ <i>James Grieve</i>	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960 58.92µCi/mg; >99% purity	SL 200	Single foliar	BBCH 69	87	1	98
	[Furanone-4- <sup>14</sup> C]-BYI 02960 53.24µCi/mg; >99% purity	SL 200			75	1	98
	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960 58.92µCi/mg; >99% purity	SL 200	Two foliar	1. BBCH 69 2. 14-d before harvest	86 Total: 172	2	14
	[Furanone-4- <sup>14</sup> C]-BYI 02960 53.24µCi/mg; >99% purity	SL 200			75 Total: 150	2	14

Soil Type		Monheim 4 (sandy loam); pH of 6.8					
Testing Environment		Glass-roofed vegetation area					
Overall TRRs in Apple Matrices							
Treatment Type		1 Foliar Application; PHI = 98 days		2 Foliar Applications; PHI = 14 days			
TRR		(ppm)		(ppm)			
Crop		[Furanone-4- <sup>14</sup> C]-BYI 02960	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960	[Furanone-4- <sup>14</sup> C]-BYI 02960	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960		
Apple fruits		0.280	0.079	1.286	0.545		
Apple leaves		38.9	56.7	102.9	134.8		
Predominant Residues (≥10% of the TRR) Expressed as Parent Equivalents							
Radiolabels		[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960; [Furanone-4- <sup>14</sup> C]-BYI 02960					
Crop		Apple Fruits		Apple Leaves			
Treatment Type		1 Foliar Application Without Surface Wash					
Analytes		% TRR	(ppm)	% TRR	(ppm)		
Parent		43.1	0.034	24.5-26.0	10.123-13.802		
Glucose/CHO		71.7	0.201	—	—		
BYI 02960-CHMP-glyc		—	—	14.4	8.141		
BYI 02960-OH-glyc		—	—	19.9-36.1	11.278-14.062		
DFA (as parent equivalents)*		0.70		1.89			
Treatment Type		2 Foliar Applications Without Surface Wash					
Analytes		% TRR	(ppm)	% TRR	(ppm)		
Parent		73.6-85.6	0.467-0.946	48.2-57.9	59.547-64.981		
Glucose/CHO		14.2	0.182	—	—		
BYI 02960-OH-glyc		—	—	15.4-17.3	17.856-20.729		
DFA (as parent equivalents)*		0.12		1.37			
*ppm equivalents = 289/95 × residue level of DFA							
Nature of the Residue in Cotton			PMRA No. 2239397, 2239398				
Crop/Variety	Radiolabel	Formulated Product	Type of Treatment	Application Details			
				Growth Stage at Application	Rate (g ai/ha)	# of appl	PHI (d)
Cotton/ <i>Gossypium hirsutum</i> , variety: Carmen	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960 118.08µCi/mg; >99% purity	SL 200	Single foliar	BBCH 15	206	1	169
	[Furanone-4- <sup>14</sup> C]-BYI 02960 106.46µCi/mg; >99% purity	SL 200			209	1	169
	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960 118.08µCi/mg; >99% purity	SL 200	Two foliar	1. BBCH 16 2. BBCH 95-99	206 + 177 Total: 383	2	15
	[Furanone-4- <sup>14</sup> C]-BYI 02960 106.46µCi/mg; >99% purity	SL 200			209 + 176 Total: 385	2	15
Soil Type		Einheitserde T (white moor peat and clay soil); pH of 5.8					
Testing Environment		Greenhouse					
Overall TRRs in Cotton Matrices							
Treatment Type		1 Foliar Application; PHI=169 days		2 Foliar Applications; PHI=14 days			
TRR		(ppm)		(ppm)			
Crop		[Furanone-4- <sup>14</sup> C]-BYI 02960	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960	[Furanone-4- <sup>14</sup> C]-BYI 02960	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960		
Intermediate Gin Trash (PHI=28 days)		12.391	14.153	—	—		
Gin Trash from mature plants		0.191	0.310	2.767	2.344		
Cotton Lint		0.009	0.007	4.993	8.846		
Cotton Seeds		0.013	0.045	0.016	0.068		
Predominant Residues (≥10% of the TRR) Expressed as Parent Equivalents							
Radiolabels		[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960; [Furanone-4- <sup>14</sup> C]-BYI 02960					
Crop		Cotton Intermediate		Gin Trash			
				Cotton Seeds			

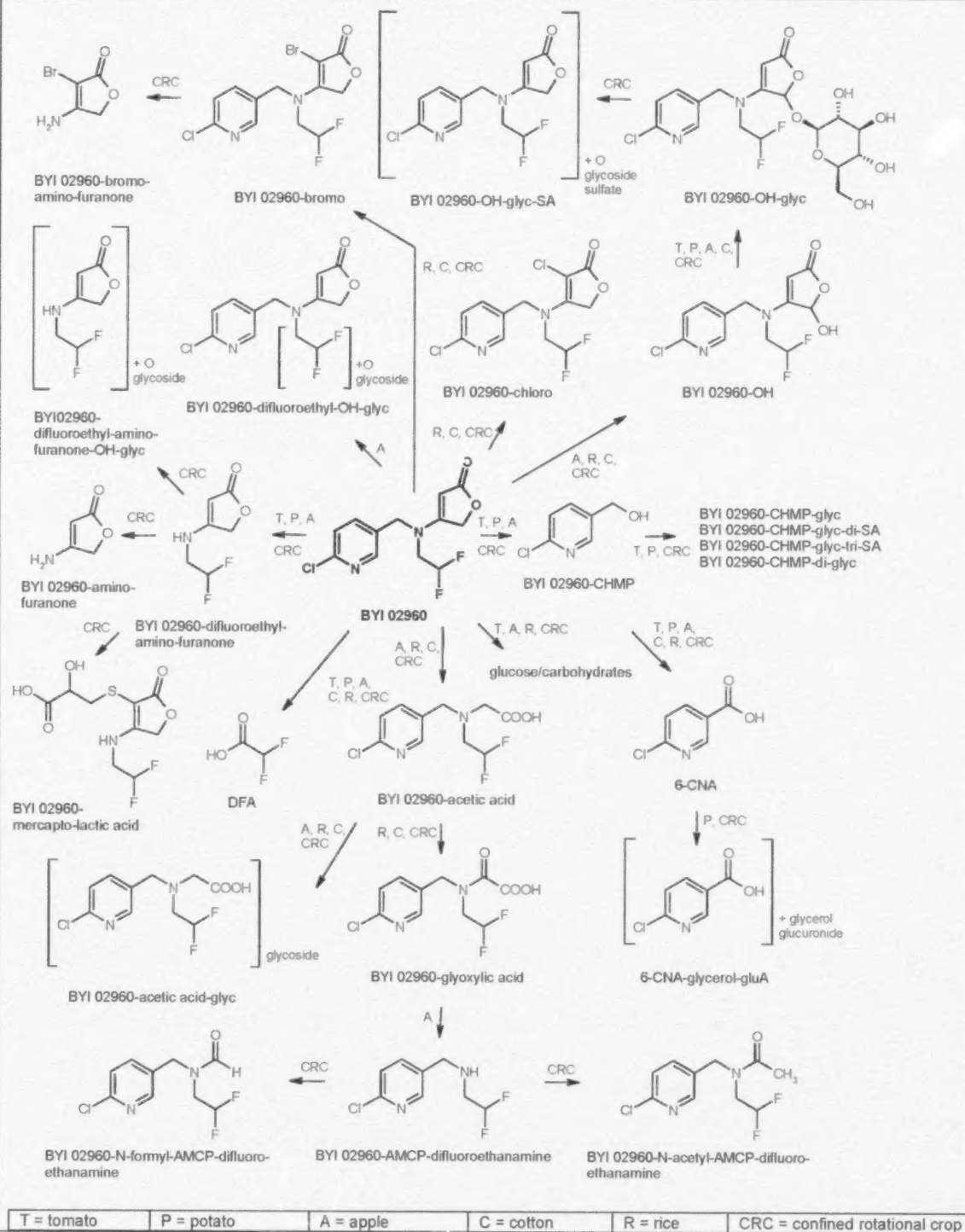


Treatment		1 Foliar Application					
Analytes		% TRR	(ppm)	% TRR	(ppm)	% TRR	(ppm)
Parent		36.9-42.3	5.22-5.24	26.3-40.0	0.076-0.082	--	--
BYI 02960-OH-glyc/acetic acid		24.9-25.1	3.08-3.56	13.7-15.7	0.030-0.043	--	--
BYI 02960-OH		--	--	13.1-14.5	0.025-0.045	--	--
BYI 02960-6-CNA		--	--	20.2	0.063	16.2	0.007
DFA (as parent equivalents)*		--		0.122		0.091	
Treatment		2 Foliar Applications					
		Cotton Gin Trash		Cotton Lint		Cotton Seeds	
Analytes		% TRR	(ppm)	% TRR	(ppm)	% TRR	(ppm)
Parent		53.2-54.4	1.25-1.51	70.3-73.0	3.51-6.46	23.4	0.016
BYI 02960-OH-glyc/acetic acid		20.8-22.4	0.53-0.58	13.9-14.6	0.69-1.30	--	--
DFA (as parent equivalents)*		0.061		--		0.061	
*ppm equivalents = 289/95 × residue level of DFA							
Nature of the Residue in Paddy Rice				PMRA No. 2239376, 2239377			
Crop/ Variety	Radiolabel	Formulated Product	Type of Treatment	Application Details			
				Growth Stage at Application	Rate (g ai/ha)	# of appl.	PHI (days)
Rice/ <i>Oryza sativa</i> L., variety: Nihonbare	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960 118.08µCi/mg; >99% purity	SL 200	Single granular/ greenhouse	BBCH 13-15	434	1	127
	[Furanone-4- <sup>14</sup> C]-BYI 02960 106.46µCi/mg; >99% purity	SL 200			409	1	127
	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960 118.08µCi/mg; >99% purity	SL 200	Two foliar/ greenhouse	1. BBCH 13-15 2. BBCH 89-92	1. 178 2. 236 Total: 414	2	29
	[Furanone-4- <sup>14</sup> C]-BYI 02960 106.46µCi/mg; >99% purity	SL 200			1. 175 2. 240 Total: 415	2	29
Soil Type		Monheim 4 (sandy loam); pH of 6.8					
Testing Environment		Greenhouse					
Overall TRRs in Paddy Rice Matrices							
Treatment Type		1 Granular/PHI = 127 days			2 Foliar/PHI=29 days		
TRR		(ppm)			(ppm)		
Crop		[Furanone-4- <sup>14</sup> C]-BYI 02960	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960		[Furanone-4- <sup>14</sup> C]-BYI 02960	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960	
Rice kernels		0.140	0.050		0.659	0.620	
Rice husks		1.404	1.602		24.098	23.957	
Rice straw		2.879	3.280		19.891	24.731	
Predominant Residues (≥10% of the TRR) Expressed as Parent Equivalents							
Radiolabels		[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960; [Furanone-4- <sup>14</sup> C]-BYI 02960					
Crop		Rice Kernels		Rice Husks		Rice Straw	
Treatment		1 Granular Treatment					
Analytes		% TRR	(ppm)	% TRR	(ppm)	% TRR	(ppm)
Parent		23.1-69.6	0.032-0.035	72.3-77.7	1.02-1.24	59.9-64.0	1.84-1.96
Glucose/CHO		26.9	0.037	--	--	--	--
BYI 02960-chloro/bromo		--	--	--	--	11.4-12.2	0.33-0.40
DFA (as parent equivalents)*		0.06		0.61		0.36	
Treatment		2 Foliar Spray Applications					
Parent		56.6-75.2	0.37-0.45	74.6-77.3	17.97-18.53	56.5-60.8	11.25-15.03
BYI 02960-chloro/bromo		--	--	--	--	10.7	2.13
DFA (as parent equivalents)*		0.24		1.40		1.19	
*ppm equivalents = 289/95 × residue level of DFA							
Nature of the Residue in Confined Rotational Crops				PMRA No. 2239458, 2239459			
EXPERIMENTAL DESIGN FOR CONFINED ROTATIONAL CROP STUDY							

Crop/crop group	Variety	PBI (days)	Growth stage at harvest	Harvested RAC	Harvesting Procedure				
Spring Wheat/Small grain	Thasos	29, 135, 296	BBCH 29-31 (end of tillering to first node at least 1 cm above tillering mode)	Forage	Approximately 20% of the plants were cut just above the soil surface				
			BBCH 79-83 (late milk to early dough stage)	Hay					
			BBCH 87-92 (hard dough to over-ripe, grain hard to very hard)	Straw and grain	The rest of the plant was cut just above the soil surface; grain was separated from straw				
Swiss chard/Leafy vegetable	Lukullus	29, 135, 296	BBCH 44-46 (40-60% of the leaf mass typical for the variety reached (immature))	Immature Stage	Some plants were cut just above the soil surface				
			BBCH 49 (typical leaf mass reached)	Mature Stage	Rest of the plants was cut just above the soil surface				
Turnips/Root crop	Rondo	29, 135, 296	BBCH 45-47 (50-70% of the expected root diameter reached)	Leaves and roots	Whole plants were removed from the soil, tops were separated from the roots				
Analytical Method Overall TRR Identification & Characterization Difluoroacetic acid (DFA)			Combustion/Liquid Scintillation Counting (LSC) LC-MS/MS LC-MS/MS residue method 01304 (non-radiolabelled DFA)						
Extraction Solvents			Acetonitrile: Water (8:2; v/v)						
Post-extraction solids (PES)			Wheat grain and straw: Microwave Assisted Extraction (60 and 100°C) Additional NaCl, diastase digestion, EDTA, cellulase digestion, HCl, and NaOH steps						
Storage Interval (harvest to analysis) at <-18°C			All samples were extracted and analysed within 9 days after harvest of the plants, with the exception of the wheat grain from the second rotation. Re-analysis of stored wheat grain confirmed the storage stability of the residues in the stored RAC for up to 21 months.						
Testing Environment	Soil Type		Formulation Type	Radiolabels	Application Rate (g ai/ha)				
Greenhouse	Sandy loam/ Monheim 4; pH of 6.9		SL 300	[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960; 118.08µCi/mg; >99% purity	436				
			SL 300	[Furanone-4- <sup>14</sup> C]-BYI 02960; 106.46µCi/mg; >99% purity	433				
Crop:		OVERALL TRR [ppm]							
Matrix:		Wheat			Swiss chard		Turnips		
		Forage	Hay	Straw	Grain	Immature	Mature	Leaves	Roots
Radiolabels		[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960 and [Furanone-4- <sup>14</sup> C]-BYI 02960							
1 <sup>st</sup> rotation- 29 days		0.78-1.41	2.00-2.41	6.29-9.02	0.18-0.48	0.85-1.36	0.87-1.48	0.68-0.82	0.07
2 <sup>nd</sup> rotation- 135 days		0.19-0.31	1.01-1.08	1.52-2.15	0.06-0.10	0.31-0.33	0.26-0.44	0.16-0.23	0.01-0.02
3 <sup>rd</sup> rotation- 296 days		0.11-0.12	0.25-0.32	0.46-0.49	0.02-0.05	0.14-0.18	0.13-0.15	0.08-0.09	0.008
PREDOMINANT RESIDUE (≥10% of the TRR): 1 <sup>st</sup> ROTATION (29 DAYS) - % of TRR (ppm)									
Parent		45.4-46.6 (0.37-0.64)	28.1-33.6 (0.67-0.68)	36.2-39.1 (2.5-3.3)	--	54.3-57.4 (0.46-0.78)	42.6-46.3 (0.37-0.69)	62.4-64.3 (0.44-0.51)	55.9-57.8 (0.04)
Glucose/CHO		--	--	--	70.5 (0.35)	--	--	--	--
BYI 02960-6-CNA-glycerol-gluA (2+3)		14.1 (0.20)	23.6 (0.57)	21.1 (1.90)	20.2 (0.04)				

Diffuoroethyl-amino-furanone	--	10.2 (0.21)	--	--	16.6 (0.14)	16.6 (0.15)	--	12.2 (0.01)
BYI 02960-glyoxylic acid	12.2-15.8 (0.12-0.17)	11.3 (0.23)	14.7-15.4 (0.93-0.97)	--	--	--	--	--
BYI-02960-OH-glyc	--	--	--	--	--	10.9-13.6 (0.12-0.16)	11.2 (0.08)	--
BYI-02960-OH	--	--	--	10.4 (0.02)	--	--	--	--
<i>DFA (ppm) as parent equivalents</i>	<i>0.274</i>	<i>0.973</i>	<i>0.608</i>	<i>3.50</i>	<i>0.243</i>	<i>0.487</i>	<i>0.243</i>	<i>0.061</i>
<b>PREDOMINANT RESIDUE (<math>\geq 10\%</math> of the TRR): 2<sup>nd</sup> ROTATION (135 DAYS) - % of TRR (ppm)</b>								
<b>Crop:</b>	<b>Wheat</b>				<b>Swiss chard</b>		<b>Turnips</b>	
<b>Matrix:</b>	<b>Forage</b>	<b>Hay</b>	<b>Straw</b>	<b>Grain</b>	<b>Immature</b>	<b>Mature</b>	<b>Leaves</b>	<b>Roots</b>
Parent	59.6-63.9 (0.12-0.18)	28.1-29.1 (0.28-0.31)	35.4-37.4 (0.54-0.80)	--	51.2-55.0 (0.17)	24.6-27.5 (0.07-0.11)	66.8-68.1 (0.11-0.15)	31.0-48.4 (-0.01)
Glucose/CHO	--	--	--	--	--	--	--	16.0 (0.002)
BYI 02960-6-CNA-glycerol-gluA (2+3)	14.4 (0.04)	23.9 (0.24)	22.0 (0.47)	11.9 (0.007)	--	--	--	--
Diffuoroethyl-amino-furanone	10.3 (0.03)	17.4 (0.05)	--	--	10.3 (0.032)	17.4 (0.046)	--	--
BYI-02960-OH-glyc	--	--	--	--	11.7-17.4 (0.04-0.06)	18.0-25.3 (0.05-0.11)	11.1-12.7 (0.02-0.03)	--
<i>DFA (ppm) as parent equivalents</i>	<i>0.061</i>	<i>0.426</i>	<i>0.183</i>	<i>0.791</i>	<i>0.122</i>	<i>0.152</i>	<i>0.091</i>	<i>0.030</i>
<b>PREDOMINANT RESIDUE (<math>\geq 10\%</math> of the TRR): 3rd ROTATION (296 DAYS) - % of TRR (ppm)</b>								
Parent	43.0-45.3 (0.05)	18.3-19.6 (0.05-0.06)	20.7-26.2 (0.10-0.13)	13.9 (0.002)	31.6-36.7 (0.04-0.07)	27.4-33.4 (0.04-0.05)	69.2-72.4 (0.06)	64.8-69.9 (0.01)
BYI 02960-bromo-amino-furanone	--	10.7 (0.027)	--	--	--	--	--	--
6-CNA-glycerol-gluA (2+3)	19.1 (0.02)	29.7 (0.10)	28.4 (0.14)	11.2 (0.002)	--	--	--	--
Diffuoroethyl-amino-furanone	12.1 (0.01)	--	--	--	13.7 (0.03)	15.6 (0.02)	--	--
BYI-02960-OH-glyc	--	--	--	--	22.2-24.6 (0.03-0.04)	21.9-28.1 (0.03-0.04)	10.2 (0.01)	--
<i>DFA (ppm) as parent equivalents</i>	<i>0.030</i>	<i>0.030</i>	<i>0.061</i>	<i>0.152</i>	<i>0.030</i>	<i>0.030</i>	<i>0.030</i>	<i>0.030</i>
Field accumulation studies were not conducted in the NAFTA regions (other than limited trials in sugarcane in Florida) since most crop that may be rotated are also petitioned for use as primary crops.								

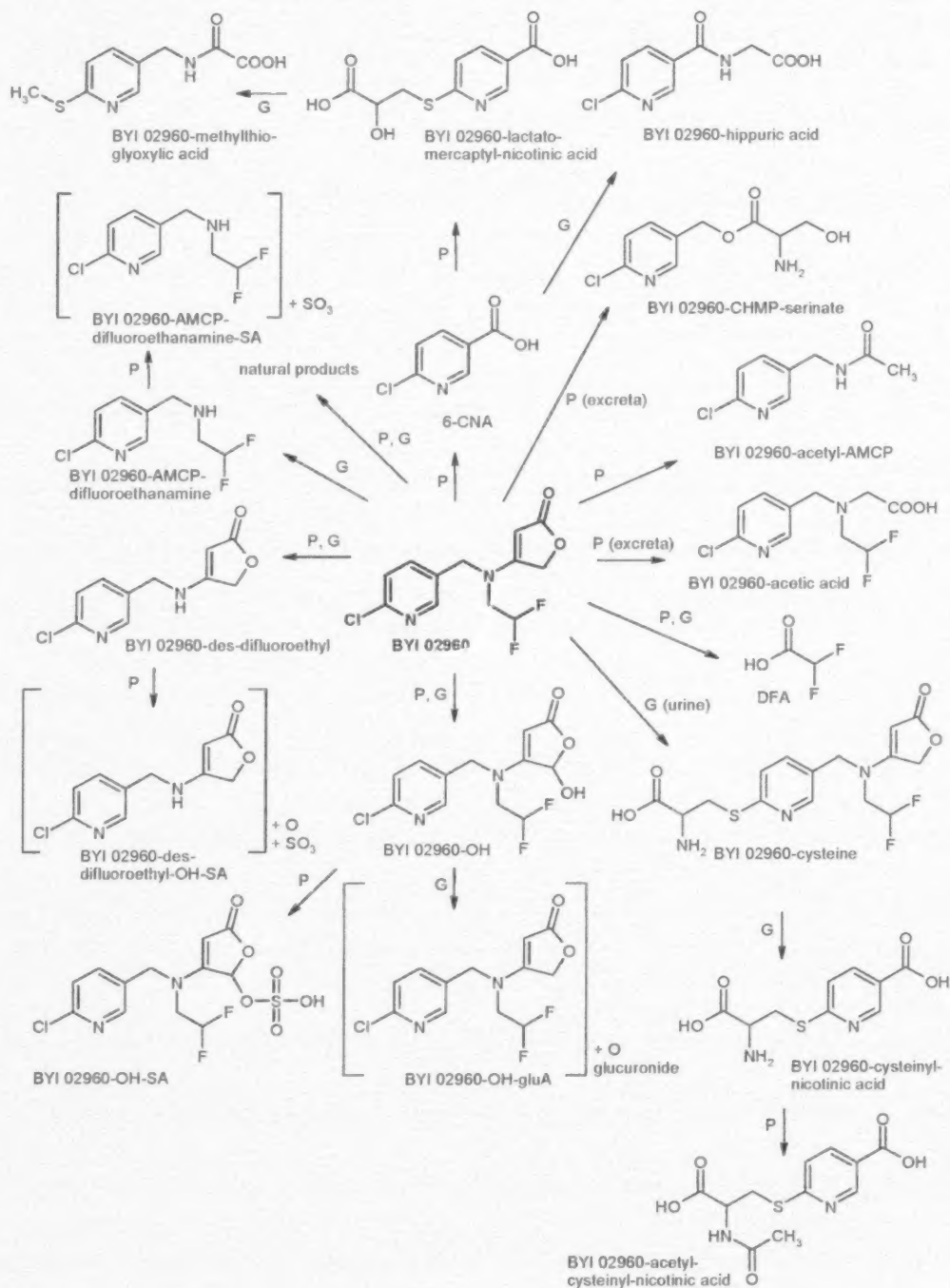
## Proposed metabolic pathway of BYI 02960 in primary and confined rotational crops.





Nature of the Residue in Laying Hen				PMRA No. 2239455, 2239457			
Group	Species	Radiolabel position	No. of animals	Application details		Sampling details	
				Dose/day (mg a.i./kg dry feed/d)	Duration (days)	Commodity	Collection Time
Laying hens ( <i>Gallus gallus domesticus</i> )	White leghorn	[pyridinylmethyl- <sup>14</sup> C] 99% purity; 94.59µCi/mg/ 27.31 Ci/mol	6/ radiolabel	16.18	14	Eggs (from ovary and oviduct)	Twice daily
		17.13		Excreta		Once daily	
				[furanone-4- <sup>14</sup> C] >99% purity; 94.59µCi/mg/ 27.31 Ci/mol		Liver, kidneys, skin, muscle (leg, thorax)	At sacrifice (6 hrs from last dose)
Analytical Method Overall TRR Identification & Characterization			Combustion/Liquid Scintillation Counting (LSC) LC-MS/MS Bayer Method RV-004-A11-04				
Extraction Solvents			4:1 (v:v) acetonitrile/water with 2.2 ml/L formic acid				
PES			Eggs/Muscle/Liver: Microwave extraction				
Storage Interval at ≤18°C			Eggs and tissues: 6.5-7 months				
Egg plateau			Pyridinylmethyl- <sup>14</sup> C: 10 days (0.09 mg/kg); Furanone-4- <sup>14</sup> C: 9 days (1.04 mg/kg)				
Overall Radioactive Residues in Laying Hen Matrices							
Matrix		[Pyridinylmethyl- <sup>14</sup> C]-BYI 02960		[Furanone-4- <sup>14</sup> C]-BYI 02960			
		% of dose	(ppm)	% of dose	(ppm)		
Liver		0.08	0.44	0.37	2.18		
Kidney		0.05	1.07	0.05	1.08		
Eggs from ovary		0.01	0.15	0.46	2.77		
Skeletal muscle		0.19	0.07	0.50	0.18		
Body skin, total		0.02	0.09	0.07	0.26		
Body fat, total		0.02	0.02	0.34	0.43		
Eggs (cumulative 13)		0.24	0.08	2.35	0.76		
Excreta, total		95.51	-	78.01	-		
Total recovery		96.49	-	83.95	-		
Predominant Residues in Laying Hen Matrices (≥10% of the TRRs)							
Radiolabels		Pyridinylmethyl- <sup>14</sup> C and Furanone-4- <sup>14</sup> C					
Matrices		Analytes		(%TRR)		(ppm)	
Eggs		Parent		19.8		0.02	
		BYI-02960-OH		18.0		0.02	
		BYI-02960-acetyl-AMCP		23.1		0.02	
Fat		Parent		15.3		0.003	
		BYI-02960-OH-SA		16.2		0.003	
		BYI-02960-acetyl-AMCP		28.5		0.006	
Liver		BYI-02960-OH-SA		22.5		0.10	
		BYI 02960-lacto-mercaptyl-nicotinic acid		15.5		0.07	
Muscle		Parent		13.6		0.005	
		BYI 02960-acetyl-AMCP		40.2		0.03	
Nature of the Residue in Lactating Goat				PMRA No. 2239480, 2239481			
Group	Species	Radiolabel position	No. of animals	Application details			
				Dose/day (mg a.i./kg dry feed/d)	Duration (days)		
Lactating goat ( <i>Capra hircus</i> )	Weibe Deutsche Edelziege	[pyridinylmethyl- <sup>14</sup> C] 99% purity; 92.57µCi/mg/ 26.72 Ci/mol	1/radiolabel	24.36	5		
		[furanone-4- <sup>14</sup> C] >99% purity; 94.59µCi/mg/ 27.31 Ci/mol		28.82			

Sampling details				
Matrices		Sampling Times		
Milk		0-8, 8-24, 24-32, 32-48, 48-56, 56-72, 72-80, 80-96, and 96-102 hrs after the first administration. Milk was collected immediately prior to each administration and about 8 hours later in the afternoon.		
Excreta		0-24, 24-48, 48-72, 72-96, and 96-102 hrs after the first administration.		
Liver, kidneys, gall bladder, muscle (loin and round), fat (omental, perirenal)		At sacrifice (6 hours from last dose)		
Analytical Method Overall TRR Identification & Characterization		Combustion/Liquid Scintillation Counting (LSC) LC-MS/MS Bayer Method RV-004-A11-04		
Extraction Solvents		4:1 (v:v) acetonitrile/water with 2.2 mL/L formic acid		
Storage Interval at $\leq 18^{\circ}\text{C}$		Milk and tissues: within 2 months		
Milk plateau		Pyridinylmethyl- $^{14}\text{C}$ : 2 days (0.05 mg/kg); Furanone-4- $^{14}\text{C}$ : 3 days (0.99 mg/kg)		
Overall Radioactive Residues in Lactating Goat Matrices				
Matrix	[Pyridinylmethyl- $^{14}\text{C}$ ]-BYI 02960		[Furanone-4- $^{14}\text{C}$ ]-BYI 02960	
	% of dose	(ppm)	% of dose	(ppm)
Liver	0.50	1.23	0.65	1.75
Kidney	0.10	1.87	0.09	1.47
Muscle	2.10	0.36	2.91	0.54
Fat	0.25	0.11	0.57	0.27
Milk (0-102 hrs)	0.78	0.19	2.58	0.96
Urine (0-102 hrs)	71.74	—	69.15	—
Feces (0-102 hrs)	13.28	—	3.00	—
Total Excreted	85.02	—	72.14	—
Total Recovery	88.75	—	78.94	—
Predominant Residues in Goat Matrices ( $\geq 10\%$ of the TRR) Expressed as Parent Equivalents				
Radiolabels		Pyridinylmethyl- $^{14}\text{C}$ and Furanone-4- $^{14}\text{C}$		
Matrices	Analytes	(%TRR)	(ppm)	
Milk	Parent	23.9-88.8	0.17-0.25	
	Lactose	66.8	0.70	
Muscle	Parent	88.1-98.0	0.35-0.48	
Fat	Parent	80.5-99.2	0.11-0.21	
Liver	Parent	59.8-84.6	1.03-1.05	
Kidney	Parent	34.8-50.5	0.65-0.74	
	BYI-02960-OH	14.6-16.0	0.22-0.30	



G = goat; P = poultry

**Storage Stability in Plants and Plant Products.****PMRA No. 2239239**

Control samples of homogenized commodities were fortified at 1.0 ppm of each BYI 02960, and DFA and stored at  $\leq -12^{\circ}\text{C}$ . Samples were analysed at approximate intervals of 1, 3, 6, and 18-month in order to capture the storage durations of samples from all field crop studies. Samples used for concurrent recoveries were prepared at the same time and stored in the same fashion as the control samples, and fortified on the day of the analysis. Storage stability recoveries were corrected to day 0.

**Summary of Flupyradifurone Stability in Various Matrix Types During Freezer Storage at  $\leq -12^{\circ}\text{C}$ .**

Matrix Type	Representative Commodities	Analytes	Demonstrated Storage Interval (months)
High-water	Spinach leaves, tomato fruit	BYI 02960, Difluoroacetic acid (DFA)	18
High-starch	Wheat grain		18
High-acid	Orange fruit		18
High-protein	Navy bean seed		18
High-oil	Coffee, soybean seed		18
Other	Sugarcane		18

The results validate the residue values reported in supervised residue trials and processing studies with respect to the storage stability of samples frozen prior to analysis.

**Storage Stability in Animal Matrices.****PMRA No. 2239063**

Samples from the livestock feeding studies were stored for less than 30 days prior to the analysis of flupyradifurone and DFA, with the exception of DFA in bovine tissues (fat, kidney, liver and muscle). To determine the freezer storage stability of DFA in bovine tissues, individual control samples of bovine fat, kidney, liver, and muscle were each fortified with DFA at 0.20 ppm and stored at  $-15^{\circ}\text{C}$ . Samples were analysed after a storage interval of 43 days in order to cover the longest period of storage during the feeding study. Samples used for concurrent recoveries were prepared at the same time and stored in the same fashion as the control samples, and fortified on the day of the analysis. Storage stability recoveries were corrected to day 0. The results validate the residue values reported in the livestock feeding studies with respect to storage stability of samples frozen prior to analysis.

**Crop Field Trials with Flupyradifurone (BYI 02960)**

The applicant submitted crop field trial data from field trials conducted in North America with a variety of crops, end-use products (SL 200, 480 FS), and different application types (foliar, soil drench, seed treatment). Adjuvants (MSO, NIS, COC) were used for all foliar treatment trials. In addition, blueberry trials (lowbush, and highbush) were conducted in North America, South America, Australia, New Zealand, and Europe using the same use pattern. For all field trials, the applicant collected residue data for flupyradifurone, difluoroacetic acid (DFA), and difluoroethyl-amino-furanone (DFEAF); however flupyradifurone and DFA were the major components of the residues in raw agricultural crop commodities (RACs). The Canada/US field trial results were generated using an adequate data collection method. Adequate storage stability data are available on diverse crop types. The number and geographic distribution of trials are generally in accordance with OCSPP harmonized test guideline 860.1500 and Health Canada's DIR98-02. Residues of flupyradifurone generally decreased with increasing PHI, but DFA often increased with PHI and reached a plateau 32-35 days after last application. Therefore, DFA was not considered an adequate marker for enforcement purposes and will not be reported herein. Data for livestock feed items that are relevant to the dietary burden estimates for Canada are included.

Crop Matrix	Applic. Rate (g ai/ha)	PHI (days)	Residues (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Root Vegetables, except Sugar Beet						PMRA No. 2239628				
GAP Foliar Application: 400 g ai/ha/season; PHI= 7d; RTI= 10d; spray volume: 100 L/ha (ground), 20 L/ha (aerial)										
Carrot	400-426	5-7	20	<0.010	0.868	<0.010	0.538	0.023	0.075	0.192
Radish	403-421	7	14	0.023	0.055	0.024	0.046	0.034	0.035	0.011
CGIC: Tuberous and Corm Vegetables						PMRA No. 2239631				
GAP Foliar Application: 400 g ai/ha/season; PHI= 7d; RTI= 10d; spray volume: 100 L/ha (ground), 20 L/ha (aerial)										
Potato Tuber	402-432	6-8	52	<0.010	0.057	<0.010	0.037	0.010	0.013	0.009



CG3-07: Bulb Vegetables			Proposed Use as Rotational Crop			PMRA No. 2239633				
Crop Matrix	Applic. Rate (g ai/ha)	PHI (days)	Residues (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Bulb Onion	405-419	12-14	24	<0.010	0.055	<0.010	0.052	0.021	0.024	0.016
Green Onion	399-422	12-14	10	0.134	1.290	0.145	1.143	0.438	0.615	0.402
CG4-13: Leafy Vegetables						PMRA No. 2239637				
GAP Foliar Application: 400 g ai/ha/season; PHI= 1d; RTI= 7d; spray volume: 100 L/ha (ground)										
Leaf lettuce	396-414	1	18	0.800	7.860	0.872	7.285	2.185	3.134	2.269
Head lettuce	407-414	1-7	16	0.220	2.350	0.306	2.315	1.165	1.261	0.712
Spinach	400-415	1	18	1.880	18.500	1.990	17.450	7.765	8.889	5.233
Mustard greens	407-421	1	16	5.820	24.300	6.075	24.250	11.900	12.960	5.735
CG5-13: Brassica (Cole) Leafy Vegetables						PMRA No. 2239638, 2239639				
GAP Foliar Application: 400 g ai/ha/season; PHI= 1d; RTI= 7d; spray volume: 100 L/ha (ground)										
Cauliflower	407-415	1-3	12	0.014	2.530	0.013	2.425	0.107	0.788	1.085
Broccoli	408-411	1	8	0.359	2.310	0.370	1.925	0.649	0.912	0.705
Cabbage	401-413	1-3	20	0.066	1.180	0.077	0.817	0.346	0.400	0.305
CG6A: Edible-Podded Legume Vegetables						PMRA No. 2239640, 2239641, 2239643				
Proposed GAP Foliar Application: 400 g ai/ha/season; PHI= 7d; RTI= 10 d; spray volume: 100 L/ha (ground), 20 L/ha (aerial)										
Snap bean	407-421	5-7	16	<0.010	0.814	0.012	0.808	0.168	0.225	0.239
Snow pea	407-452	6-7	12	0.491	1.290	0.577	1.205	0.945	0.874	0.249
Succulent Shelled Pea and Beans										
Garden pea	407-422	7	12	0.120	0.788	0.125	0.773	0.558	0.508	0.258
Lima bean	408-416	6-7	18	<0.010	0.118	0.010	0.115	0.020	0.041	0.041
CG6C: Dried Shelled Pea and Bean (except soybean)										
Pea seed	409-415	7-28	20	0.014	1.470	0.017	1.325	0.553	0.645	0.440
Pea green vines		7-28	20	1.450	6.200	1.515	5.740	4.240	3.987	1.170
Pea hay		5-7	20	4.600	18.300	4.690	15.100	7.815	8.336	3.163
Bean seed	405-419	7-28	18	<0.010	0.249	0.010	0.244	0.036	0.065	0.074
Bean hay		3-14	18	<0.010	10.500	0.040	9.820	3.545	4.296	3.408
Bean forage		6-7	18	0.032	2.460	0.055	2.340	0.796	1.005	0.756
Dry Soybeans						PMRA No. 2239644				
GAP Foliar Application: 400 g ai/ha/season; PHI= 21 d; RTI= 10 d; spray volume: 100 L/ha (ground), 20 L/ha (aerial); Proposed GAP Seed Treatment: 16.9-25.4 g ai/ha (based on planting rate of 370,000 dry soybeans/ha)										
Dry soybeans (Foliar)	403-428	19-28	40	<0.010	1.100	<0.010	1.020	0.060	0.165	0.252
Soybean hay		5-7	40	1.23	19.70	1.46	17.36	7.11	7.96	4.05
Soybean forage		5-7	40	0.87	7.65	0.94	6.77	3.19	3.30	1.50
Dry soybeans (Seed Treatment)	32-51	131-138	6	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010	0.000
Soybean hay		58-72	6	<0.010	0.140	0.01	0.120	0.025	0.052	0.055
Soybean forage		58-72	6	<0.010	0.080	0.01	0.070	0.030	0.037	0.029
CG8-09: Fruiting Vegetables						PMRA No. 2239645				
GAP Foliar Application: 400 g ai/ha/season; PHI= 1 d; RTI= 7 d; spray volume: 100 L/ha (ground). Same application rate proposed for soil treatment with PHI = 45 d										
Tomato (Foliar)	404-413	1-7	38	0.050	0.601	0.057	0.570	0.134	0.191	0.147
Tomato (Soil)	394-419	43-45	38	<0.010	0.357	0.010	0.236	0.012	0.029	0.059
Bell pepper (Foliar)	399-418	1	20	0.016	0.546	0.030	0.474	0.099	0.151	0.136
Bell pepper (Soil)	394-411	45	20	<0.010	0.251	<0.010	0.242	0.012	0.039	0.072

Crop Matrix	Applic. Rate (g ai/ha)	PHI (days)	Residues (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Non-bell pepper (Foliar)	415-422	1	8	0.063	0.576	0.073	0.529	0.228	0.265	0.208
Non-bell pepper (Soil)	408-419	45	8	<0.010	0.048	0.010	0.047	0.016	0.022	0.016
<b>CG9: Cucurbit Vegetables</b>							<b>PMRA No. 2239681</b>			
GAP Foliar Application: 409 g ai/ha/season; PHI=1d; RTI= 10d; spray volume: 9.46 L/ha (ground), 7.57 L/ha (aerial); applied as diluted or concentrated spray; Same application rate proposed for soil treatment with PHI= 30 d.										
Cucumber (Foliar)	403-418	1	18	0.034	0.248	0.039	0.225	0.101	0.117	0.061
Cucumber (Soil)	408-413	19-21	18	<0.010	0.032	0.010	0.027	0.010	0.013	0.006
Melon (Foliar)	395-419	1	10	0.060	0.202	0.061	0.186	0.116	0.119	0.048
Melon (Soil)	409-410	21-28	10	<0.010	0.028	<0.010	0.028	0.014	0.016	0.007
Summer squash (Foliar)	401-423	1-7	16	0.021	0.114	0.033	0.100	0.057	0.060	0.025
Summer squash (Soil)	408-414	19-28	16	<0.010	0.095	0.010	0.057	0.010	0.020	0.021
<b>CG10-Revised: Citrus Fruits</b>							<b>PMRA No. 2239685</b>			
GAP Foliar Application: 409 g ai/ha/season; PHI=1d; RTI= 10d; spray volume: 9.46 L/ha (ground), 7.57 L/ha (aerial); applied as diluted or concentrated spray. Same application rate proposed for soil treatment with PHI= 30d.										
Orange (Foliar)	386-423	1-10	24	0.020	2.080	0.153	1.245	0.231	0.431	0.506
Orange (Soil)	404-427	30	24	<0.010	0.041	0.010	0.031	0.010	0.014	0.008
Lemon (Foliar)	402-426	1-10	16	0.037	0.713	0.089	0.484	0.232	0.269	0.201
Lemon (Soil)	398-410	30	16	<0.010	<0.010	<0.010	<0.010	0.010	0.010	0.000
Grapefruit (Foliar)	407-427	1-3	12	0.062	0.287	0.124	0.206	0.175	0.178	0.061
Grapefruit (Soil)	403-414	30	12	<0.010	0.056	0.010	0.049	0.014	0.022	0.017
<b>CG11-09: Pome Fruits</b>							<b>PMRA No. 2239686</b>			
GAP Foliar Application: 400 g ai/ha/season; PHI= 14d; RTI= 10d; spray volume: 100 L/ha (ground); applied as diluted or concentrated spray										
Apple	403-425	14-21	28	0.016	0.296	0.067	0.253	0.118	0.134	0.071
Pear	403-430	14	18	0.059	0.467	0.128	0.338	0.200	0.218	0.094
<b>CG13-07B: Bushberry</b>							<b>PMRA No. 2239687</b>			
GAP Foliar Application: 400 g ai/ha/season; PHI= 3d; RTI= 7d; spray volume: 100 L/ha (ground)										
Blueberry - Global	329-428	3-7	52	0.131	2.535	0.133	2.479	0.791	0.928	0.640
<b>CG13-07F: Small Fruit Vine Climbing Subgroup, except Fuzzy Kiwifruit</b>							<b>PMRA No. 2239688</b>			
GAP Foliar Application: 400 g ai/ha/season; PHI= 0d; RTI= 7d; spray volume: 100 L/ha (ground). Same application rate for soil treatment with PHI= 30d.										
Grape (Foliar)	388-417	0-3	32	0.242	2.280	0.314	1.900	0.508	0.647	0.429
Grape (Soil)	408-426	28-30	32	<0.010	0.049	0.010	0.040	0.010	0.013	0.008
<b>CG13-07G: Low Growing Berry</b>							<b>PMRA No. 2239689</b>			
GAP Foliar Application: 400 g ai/ha/season; PHI= 3d; RTI= 7d; spray volume: 100 L/ha (ground)										
Strawberry	399-415	0	20	0.211	0.638	0.227	0.619	0.444	0.453	0.127
<b>CG14-11: Tree Nuts</b>							<b>PMRA No. 2239691</b>			
GAP Foliar Application: 400 g ai/ha/season; PHI= 7d; RTI= 14d; spray volume: 100 L/ha (ground); applied as diluted or concentrated spray										
Pecan nutmeat	406-421	7	20	<0.010	0.013	0.010	0.012	0.010	0.010	0.001
Almond nutmeat	403-421	7	20	<0.010	0.015	0.010	0.015	0.010	0.011	0.002
Almond hulls	403-421	7	10	0.195	6.16	0.026	5.31	1.70	2.32	2.13

Hops (Dried)							PMRA No. 2239706			
GAP Foliar Application: Proposed GAP Foliar Application: 150 g ai/ha/season; PHI= 21d; spray volume: 100 L/ha (ground); applied as diluted or concentrated spray										
Crop Matrix	Applic. Rate (g ai/ha)	PHI (days)	Residues (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Hops (dried)	152-156	21	6	2.180	4.720	2.300	4.675	2.555	3.150	1.195
Green Coffee Beans							PMRA No. 2239705, 2239735			
GAP Foliar Application: 600 g ai/ha/season; PHI= 0d; RTI= 15d; spray volume: 1 L/ha; Proposed Soil Drench: 600 g ai/ha/season; PHI= 21d; spray volume: 3 L/ha (ground)										
Green Coffee Bean	1200	0-28	16	0.02	0.588	0.020	0.552	0.069	0.141	0.170
Prickly Pear Cactus							PMRA No. 2239708			
GAP Foliar Application: 409 g ai/ha/season; PHI=14d; RTI= 7d; spray volume: 284 L/ha (ground)										
Prickly pears	359-374	20-21	8	0.047	0.152	0.068	0.123	0.101	0.102	0.032
Prickly pear pads	369-376	20-21	8	0.154	0.271	0.204	0.254	0.226	0.222	0.036
Peanut							PMRA No. 2239707			
Proposed GAP Foliar Application: 400 g ai/ha/season; PHI= 7d; RTI= 10d; spray volume: 100 L/ha (ground)										
Peanut nutmeat	397-421	7-14	24	<0.010	0.034	0.010	0.027	0.010	0.012	0.006
Peanut hay	397-421	7-14	24	1.65	16.90	1.66	11.20	5.27	6.21	3.86
CG15: Cereal Grains							PMRA No. 2239692, 2239695, 2239696, 2239698			
GAP Foliar Application: 400 g ai/ha/season; PHI Forage= 7d, PHI Grain, Straw, Stover= 21d; Sweet corn kernel =7d; RTI= 7d; spray volume: 100 L/ha (ground), 20 L/ha (aerial) for corn; 37.85 L/ha (ground), 7.57 L/ha (aerial) for barley, wheat, and sorghum.										
Field corn grain	405-423	20-21	40	<0.010	0.011	<0.010	0.011	0.010	0.010	0.000
Field corn forage		5-7	40	0.594	4.110	0.686	3.975	2.010	2.192	0.798
Field corn stover	405-419	20-21	40	0.649	6.100	0.900	5.900	1.630	2.152	1.298
Sweet corn grain		19-21	26	<0.010	0.047	<0.010	0.038	0.010	0.014	0.009
Sweet corn forage		5-7	26	0.050	10.200	0.050	9.190	1.840	2.423	2.265
Sweet corn stover		19-21	26	0.454	9.220	0.528	8.160	2.805	2.916	2.076
Barley	401-417	21-35	40	0.033	2.360	0.038	2.255	0.454	0.600	0.559
Sorghum	406-420	21-26	18	0.322	1.800	0.337	1.530	0.545	0.755	0.429
Wheat	399-423	21-35	58	0.012	0.749	0.017	0.729	0.110	0.182	0.186
CG20C: Undelinted Cotton Seed							PMRA No. 2239699			
GAP Foliar Application: 409 g ai/ha/season; PHI= 14d; RTI= 14d; spray volume: 37.85 L/ha (ground), 7.57 L/ha (aerial)										
Undelinted Seed	406-425	13-14	22	<0.010	0.632	0.014	0.397	0.080	0.129	0.153
CG22B: Leaf Petiole Vegetables							PMRA No. 2239367			
GAP Foliar Application: 400 g ai/ha/season; PHI= 1d; RTI= 7d; spray volume: 100 L/ha										
Celery	402-415	1	20	0.170	6.680	0.221	5.985	2.170	2.312	1.640
Alfalfa							PMRA No. 2239703			
GAP Foliar Application: 400 g ai/ha/season; PHI= 7d; RTI= 9d; spray volume: 93-467 L/ha										
Alfalfa forage	402-416	5-7	26	0.427	8.69	0.442	7.87	3.08	3.15	1.88
Alfalfa hay	402-416	5-7	26	2.41	11.2	2.54	9.48	6.14	6.41	2.36

**Processed Food and Feed**

Processing studies were conducted with raw agricultural commodities treated with flupyradifurone during the magnitude of the residue trials, while simulating commercial practices as closely as possible. Concurrent recoveries were conducted to validate the analytical method for flupyradifurone and DFA in the various processed commodities. Results of DFA are not presented herein as it is not part of the residue definition for enforcement.

Raw Agricultural Commodity	Processed Commodity	Processing Factor	Anticipated Residue	PMRA No.
<b>Field Corn</b> [HAFT = 0.011 ppm]	Aspirated grain fractions	23.43	0.26	2239745
	Bran	2.82	0.03	
	Flour	0.64	0.01	
	Germ (dry milling)	1.03	0.01	
	Germ (wet milling)	0.71	0.01	
	Grits	0.64	0.01	
	Meal (dry milled)	0.66	0.01	
	Oil (dry milled)	0.64	0.01	
	Starch	0.64	0.01	
<b>Wheat</b> [HAFT = 0.729 ppm]	Aspirated grain fractions	17.65	12.87	2239754
	Bran	2.35	1.71	
	Germ	1.65	1.20	
	Gluten	0.36	0.26	
	Middling	0.7	0.51	
	Shorts	0.92	0.67	
	Starch	0.01	0.01	
	White flour	0.27	0.20	
	Wheat whole meal flour	1.2	0.88	
<b>Peanut</b> [HAFT = 0.027 ppm]	Meal	1.65	0.05	2239750
	Refined oil	0.5	0.01	
	Peanut butter	0.56	0.02	
	Dry roasted peanuts	0.55	0.02	
<b>Undelinted Cotton Seed</b> [HAFT = 0.397 ppm]	Meal	0.14	0.06	2239747
	Hulls	0.52	0.21	
	Refined oil	0.02	0.01	
<b>Orange</b> [HAFT = 1.25 ppm]	Juice	0.03	0.04	2239749
	Oil	0.02	0.03	
	Pulp	1.02	1.28	
	Wet pomace	1.20	1.50	
	Dried pomace	4.60	5.75	
	Marmalade	0.02	0.03	
	Sauce	0.74	0.19	
<b>Apple</b> [HAFT = 0.253 ppm]	Wet pomace	1.49	0.38	2239740
	Dried pomace	4.83	1.22	
	Juice	0.49	0.12	
	Pomace	1.76	3.34	
<b>Grape</b> [HAFT = 1.90 ppm]	Wine	0.53	1.01	2239748
	Jelly	0.28	0.53	
	Raisins	2.48	4.71	
	Juice	0.66	1.25	
	Juice	0.65	0.37	
<b>Tomato</b> [HAFT = 0.570 ppm]	Peeled	0.60	0.25	2239753
	Purée	1.32	0.75	
	Paste	2.00	1.14	
	Preserve	0.68	0.39	
	Dried	2.00	1.14	
	Crisps	0.83	0.03	
<b>Potato</b> [HAFT = 0.037 ppm]	Flakes	0.98	0.04	2239751
	Wet potato peel	0.98	0.04	
	Starch	0.83	0.03	
	Peeled tuber	0.83	0.03	



Raw Agricultural Commodity		Processed Commodity		Processing Factor		Anticipated Residue		PMRA No.
Soybean [HAFT = 1.020 ppm]		Aspirated grain fractions		13.80		14.06		2239752
		Meal		1.05		1.07		
		Hulls		0.98		1.00		
		Refined oil		0.02		0.02		
		Milk		0.07		0.07		
		Flour		1.12		1.14		
Hop (dried cone) [HAFT = 4.68 ppm]		Draff		0.03		0.16		2239756
		Brewer's yeast		0.03		0.16		
		Beer		0.01		0.02		
Green Bean Coffee [HAFT = 0.552 ppm]		Roasted coffee bean		0.59		0.33		2239742
		Instant coffee		2.06		1.13		
Laying Hen Feeding Study Design.						PMRA No. 2239073		
Species	Age/Weight at Dosing	Average Feed Consumption	# Animals/ Subgroups	Application details		Sampling details		
				Rate (ppm feed)	Duration (days)	Commodity		Collection Time
Laying hens (White leghorn)	34 weeks old/1153-1640 grams	128.0 g/bird/day	Group 1: 24/6 Group 2: 12/3 Group 3: 12/3 Group 4: 12/3 Group 5: 24/6	Group 1: 0 Group 2: 1.5 Group 3: 6.5 Group 4: 19.4 Group 5: 65.1	28	Eggs		Twice daily (a.m. and p.m.)
						Liver, muscle (thigh, breast), fat (abdominal with skin, subcutaneous)		After sacrifice (<5 hours)
Matrices		Sampling Day		Feeding Level (ppm)	Flupyradifurone Residues (ppm)			
					n	Min	Max	Mean
Whole Eggs		28		1.5	3	0.010	0.010	0.010
		28		6.5	3	0.010	0.010	0.010
		28		19.4	3	0.010	0.040	0.023
		28		65.1	12	0.067	0.283	0.173
Whole Egg Depuration		35		65.1	3	0.010	0.010	0.010
		42		65.1	2	0.010	0.010	0.010
		49		65.1	1	0.010	0.010	--
Fat		29		1.5	3	0.010	0.010	0.010
		29		6.5	3	0.010	0.010	0.010
		29		19.4	3	0.010	0.010	0.010
		29		65.1	3	0.010	0.555	0.193
Fat Depuration		35		65.1	1	0.010	0.010	--
		42		65.1	1	0.010	0.010	--
		49		65.1	1	0.010	0.010	--
Liver		29		1.5	3	0.010	0.010	0.010
		29		6.5	3	0.010	0.011	0.011
		29		19.4	3	0.010	0.010	0.010
		29		65.1	3	0.010	0.061	0.033
Liver Depuration		35		65.1	1	0.010	0.010	--
		42		65.1	1	0.010	0.010	--
		49		65.1	1	0.010	0.010	--
Muscle		29		1.5	3	0.010	0.010	0.010
		29		6.5	3	0.010	0.010	0.010
		29		19.4	3	0.010	0.010	0.010
		29		65.1	3	0.010	0.058	0.039
Muscle Depuration		35		65.1	1	0.010	0.010	--
		42		65.1	1	0.010	0.010	--
		49		65.1	1	0.010	0.010	--

Overall Assessment of Laying Hen Feeding Study							
When laying hens were fed flupyradifurone at 1.5 ppm, 6.5 ppm, 19.4 ppm, and 65.1 ppm, residues of parent were dose-dependent. Residues of flupyradifurone reached a maximum at day 28 of the highest feeding level in whole eggs. Following cessation of dosing, residues declined to less than LOQ by day 35 in all tissues. The highest to lowest maximum residues of flupyradifurone were found in fat (0.555 ppm), whole eggs (0.283 ppm), liver (0.061 ppm), and muscle (0.058 ppm) at the 65.1 ppm feeding level.							
Lactating Cow Feeding Study Design.						PMRA No. 2239063	
Species	Age/Weight at Dosing	Average Feed Consumption	# Animals	Application details		Sampling details	
				Rate (ppm feed)	Duration (days)	Commodity	Collection Time
Lactating Dairy Cow (Holstein)	2.5-3.5 years old/ 461.7-612.8 kg	20.2 kg/cow/day (dry weight)	Group 1: 2 Group 2: 4 Group 3: 3 Group 4: 3 Group 5: 7	Group 1: 0 Group 2: 4.81 Group 3: 23.1 Group 4: 49.6 Group 5: 135	28	Milk	Collected twice daily in the evening and following morning prior to dosing.
						Liver, kidney, fat, and muscle	At sacrifice (at least 3 hours after last dose)
Matrices	Sampling Day	Feeding Level (ppm)	Flupyradifurone Residues (ppm)				
			n	Min	Max	Mean	
Whole Milk	28	4.81	4	0.019	0.026	0.023	
	28	23.1	3	0.090	0.125	0.108	
	28	49.6	3	0.238	0.290	0.267	
	28	135	7	0.615	0.919	0.748	
Whole Milk Depuration	30	135	3	0.043	0.071	0.059	
	31	135	3	0.010	0.010	0.010	
	35	135	2	0.010	0.010	0.010	
Fat	29	4.81	4	0.017	0.028	0.021	
	29	23.1	3	0.097	0.120	0.109	
	29	49.6	3	0.231	0.377	0.285	
	29	135	4	0.767	1.370	0.977	
Fat Depuration	32	135	1	0.010	0.010	--	
	36	135	1	0.010	0.010	--	
	43	135	1	0.010	0.010	--	
Liver	29	4.81	4	0.119	0.172	0.145	
	29	23.1	3	0.714	0.821	0.755	
	29	49.6	3	0.106	0.169	1.680	
	29	135	4	2.960	3.890	3.450	
Liver Depuration	32	135	1	0.033	0.033	--	
	36	135	1	0.010	0.010	--	
	43	135	1	0.010	0.010	--	
Kidney	29	4.81	4	0.122	0.222	0.159	
	29	23.1	3	0.711	0.894	0.786	
	29	49.6	3	1.310	2.150	1.790	
	29	135	4	4.160	5.660	4.720	
Kidney Depuration	32	135	1	0.045	0.045	--	
	36	135	1	0.010	0.010	--	
	43	135	1	0.010	0.010	--	

Matrices	Sampling Day	Feeding Level (ppm)	Flupyradifurone Residues (ppm)			
			n	Min	Max	Mean
Muscle	29	4.81	4	0.038	0.048	0.043
	29	23.1	3	0.242	0.260	0.250
	29	49.6	3	0.490	0.740	0.597
	29	135	4	1.250	1.880	1.505
Muscle Depuration	32	135	1	0.017	0.017	—
	36	135	1	0.010	0.010	—
	43	135	1	0.010	0.010	—
<b>Overall Assessment of Dairy Cattle Feeding Study.</b>						
When dairy cattle were fed flupyradifurone at 4.81 ppm, 23.1 ppm, 49.6 ppm, and 135 ppm, residues of parent were dose-dependent. Residues of parent reached a maximum at day 17 in milk. Following cessation of dosing, residues declined to less than LOQ by day 31 (milk, fat), and day 36 (kidney, liver, muscle). The highest to lowest maximum residues of flupyradifurone were found in kidney (5.66 ppm), liver (3.89 ppm), muscle (1.88 ppm), and fat (1.37 ppm) at the 135 ppm feeding level.						
<b>Dietary Burden and Anticipated Residues in Fat, Meat, Meat byproducts, Milk, and Eggs for Enforcement.</b>						
The livestock feedstuff items associated with the proposed uses in Canada include alfalfa, almonds, apples, carrots, corn (field, popcorn and sweet), peas, beans, potatoes, and soybeans. The highest values or median values for residues of flupyradifurone were used in the calculations as prescribed.						
Matrix Type		Dietary Burden (ppm)	Highest Residue (ppm)	Feeding Level Closest to DB	Anticipated Residues (MRL purposes)	
Poultry	Fat	0.43	0.01	1.5	0.003	
	Liver		0.01	1.5	0.003	
	Muscle		0.01	1.5	0.003	
	Eggs		0.01	1.5	0.003	
Dairy cattle	Fat	11.06	0.120	23.1	0.057	
	Liver		0.821	23.1	0.393	
	Kidney		0.894	23.1	0.426	
	Muscle		0.260	23.1	0.124	
	Milk		0.125	23.1	0.060	
Swine	Fat	0.38	0.028	4.81	0.002	
	Liver		0.172	4.81	0.014	
	Kidney		0.222	4.81	0.018	
	Muscle		0.048	4.81	0.004	

Table 10 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

Matrices	Rationale
<b>Primary crops</b> (Apple, cotton, paddy rice, tomato, potato)	Flupyradifurone, CHMP-di-glyc, 6-CNA, and DFA were identified as major residues in the primary crop metabolism studies and/or crop field trials. CHMP-di-glyc and 6-CNA were not characterised as being of toxicological concern, and are expected to be rapidly metabolized and conjugated. Therefore, parent is a suitable marker for enforcement purposes as it is present in all plant commodities at quantifiable levels. DFA was also present in primary and secondary crops, but tends to increase with time making it an unsuitable marker compound for enforcement. However, given the comparable toxicities of parent and DFA and the relative amounts of both found in plant metabolism, secondary crops and crop field trials, the sum of flupyradifurone and DFA, expressed as parent equivalents, is the recommended residue definition for commodities of plant origin for dietary exposure assessment.
<b>Secondary crops</b> (Wheat, Swiss chard, turnips)	
<b>Residue Definition in Food of Plant Origin:</b>	<u>Enforcement:</u> Flupyradifurone <u>Dietary Exposure:</u> Flupyradifurone and DFA, expressed as parent equivalents



<b>Ruminant (Lactating goat)</b>	Flupyradifurone and DFA were the main residues identified in the ruminant metabolism and feeding studies. Since flupyradifurone was observed in the feeding study, it is considered an appropriate marker for enforcement. Given the comparable toxicities of parent and DFA and the relative amounts of both found in the feeding study, a residue definition of the sum of flupyradifurone and DFA, expressed as parent equivalents is recommended for ruminant commodities for dietary exposure assessment.
<b>Poultry (Laying hens)</b>	The poultry feeding study showed DFA as the predominant residue, and flupyradifurone and several metabolites at low concentrations relative to DFA. Flupyradifurone is predicted to be at or below the LOQ of the analytical method in poultry commodities at the estimated dietary burden for poultry. DFA may be slightly above the LOQ in some poultry commodities at the dietary burden level, however there is no justification to include it as a marker for enforcement. In addition, the lack of a DFA feeding study does not allow for accurate determination of the DFA residue contribution from DFA itself. Given the comparable toxicities of parent and DFA and the relative amounts of both found in the feeding study, a residue definition of the sum of flupyradifurone and DFA, expressed as parent equivalents is recommended for poultry commodities for dietary exposure assessment.
<b>Residue Definition in Food of Animal Origin:</b>	<u>Enforcement:</u> Flupyradifurone <u>Dietary Exposure:</u> Flupyradifurone and DFA, expressed as parent equivalents
<b>Fat Soluble Residue:</b>	No
<b>Similarity of metabolic profile</b>	
<b>Plants</b>	The metabolic pathways in the five crops, irrespective of application types (soil, foliar, seed) are qualitatively similar and well understood based on characterization and identification of the residues. The metabolic pathway in confined rotational crops is similar to that in primary crops. Flupyradifurone is generally the predominant residue, including DFA, which was observed in all plant metabolism studies. DFA is also a rat metabolite.
<b>Livestock</b>	The metabolism in ruminants qualitatively mirrors that of plants. Metabolism is limited, with flupyradifurone as the predominant residue in all commodities. In milk, complete degradation of the parent (degradation of the furanone moiety) and reincorporation is indicated by the presence of radiolabeled lactose. Other metabolic pathways are indicated by the presence of 6-CNA from the cleavage of the pyridinylmethylamine bond and the presence of BYI 02960-OH-gluA from hydroxylation of the furanone moiety. The metabolism in poultry is much more extensive than in plants or ruminants, as evidenced by the low or no concentrations of flupyradifurone in eggs and tissues. The majority of the radiolabeled residue was characterized as fatty acids. The majority of the minor metabolites found are consistent with metabolites found in the ruminant and in the rat.

**Refined Chronic Dietary Risk from Food and Water: Sum of Parent and DFA, expressed as Parent Equivalents.**

Flupyradifurone End-Point Parameters	POPULATION	Estimated Risk % of Acceptable Daily Intake (ADI)	
		Food Only	Food and Water EEC = 0.264 ppm
ADI = 0.08 mg/kg bw/day	Total Population	4.9	11.9
	All infants < 1 year	8.0	30.8
	Children 1-2 years	15.1	25.5
	Children 3-5 years	11.7	21.3



	Children 6-12 years	6.8	13.5
	Youth 13-19 years	4.0	9.0
	Adults 20-49 years	3.7	10.2
	Adults 50+ years	4.0	10.8
	Females 13-49	3.6	10.1
<b>Refined Acute Dietary Risk from Food and Water: Sum of Parent and DFA, expressed as Parent Equivalents.</b>			
Flupyradifurone End-Point Parameters	POPULATION	Estimated Risk % of Acute Reference Dose (ARfD)	
		Food Only	Food and Water EEC = 0.267 ppm
<b>ARfD<sub>13-49</sub> = 0.13 mg/kg bw/day</b> <b>ARfD<sub>Total</sub> = 0.35 mg/kg bw/day</b>	All infants < 1 year	13.7	22.3
	Children 1-2 years	21.6	25.5
	Children 3 to 5 years	16.8	20.1
	Children 6-12 years	10.7	13.0
	Males 13-19 years	7.0	9.6
	Males 20-49 years	6.2	8.7
	Adults 50+ years	6.6	8.9
	Females 13-49 years	16.7	24.0

**Table 11 Postapplication risk assessment for flupyradifurone (shading indicates target MOE not exceeded)**

Crop / CG	Application Rate ( $\mu\text{g}/\text{cm}^2$ )	TC ( $\text{cm}^2/\text{hr}$ )	Exposure ( $\text{mg}/\text{kg}$ bw/day)	REI (days) <sup>1</sup>	MOE <sup>2</sup>
CG 1, 2, 6, 8, 9, 13 G, Peanut	2	1750	0.0106	0	734
CG 4, 13 B	2	1750	0.0116	0	670
CG 5	2	5150	0.0308	1	253
		4400	0.0293	0	266
CG 11	2	3000	0.0182	0	428
CG 13 F	1.5	19300	0.0878	0	89
		8500	0.0387	0	202
CG 14	1.5	580	0.0024	0	3240
Corn	1.5	8800	0.0439	0	178
Alfalfa	1.5	1750	0.0059	0	1320
Hops	1.5	19300	0.0071	21	1094
		1750	0.0059	0	1320

<sup>1</sup> REI of 0 days used to calculate the worst-case exposure scenario

<sup>2</sup> MOE = NOAEL of 7.8 mg/kg bw/day; Target MOE = 100

Table 12 Summary of fate and behaviour of flupyradifurone in the environment

Property	Test substance	DT <sub>50</sub> /t <sub>1/2- rep</sub> (days)	Major transformation products	Comments/classification	PMRA#
Abiotic transformation					
Hydrolysis	BYI 02960	stable	none	Not an important route	2239095
Phototransformation on soil	BYI 02960	449	none	Not an important route	2239479
Phototransformation in water	BYI 02960	1.8 – 3.8	BYI 02960-succinamide (max. 38.3-39.7%) BYI 02960-azabicyclosuccinamide (max. 14.8-27.3%)	May contribute to overall dissipation	2239100 2239102
Phototransformation in air	BYI 02960	1.8 – 0.55	NA	Modelling results. Long-range transport is not expected.	2239160
Biotransformation in soil					
Biotransformation in aerobic soil	BYI 02960	62.9 / 178	DFA (max. 22.0-33.9% AR)	Moderately persistent	2239344
		37.5 /78.4	none	Slightly persistent	2239361
		112 /194	none	Moderately persistent	2239357
		45.4 /75	none	Moderately persistent	2239360
		215 / 227	none	Persistent	2239358
		56.6 / 114	none	Moderately persistent	2239359
		134 – 401 / 97.9 - 484	none	Moderately persistent - persistent	2239366
	6-CNA	2.7-6.5 / 2.1-4.0	none	Non-persistent	2239478
Biotransformation in anaerobic soil	BYI 02960	693 / 693	25.1% DFA formed in the aerobic phase of the study	Persistent	2239452
		631 / 631	11.4% 6-CNA formed in aerobic phase of the study	Persistent	2239453
		582 / 582	none	Persistent	2239454
Mobility					
Property	Test substance	K <sub>d</sub> /K <sub>oc</sub>	Comment	Mobility classification	PMRA#
Adsorption in soil	BYI 02960	2.19-4.12 / 80.7-113.9	4 German soils	High mobility	2239343
		0.63-2.82 / 89.5-148.6	2 US soils	High mobility	2239342
		0.65-22.07 / 86.0-283.0	4 Brazilian soils	Moderate to high mobility	2239345
		4.58±6.43 / 137.1±72.1	Mean	High mobility	
	DFA	0.17±0.14 / 6.33±2.85	Mean (3 German soils and 2 US soils)	Very high	2239449
	6-CNA	0.94±0.50 / 112.9±70.9	Mean (5 US soils)	High	2239450

Property		Test substance	DT <sub>50</sub> /t <sub>1/2-rep</sub> (days)	Major transformation products	Comments/classification	PMRA#
Soil leaching		BYI 02960		Relative to mobility of monuron (4 Brazilian soils)	Moderate to high mobility	2239476
Volatilization		Not expected based on vapour pressure and Henry's law constant				
Field dissipation						
Test site		Test item and rate	DT <sub>50</sub> /t <sub>1/2-rep</sub> (days)	Major transformation products	Comments/classification	PMRA#
Field dissipation	CA	BYI	55.9 / 329	none	Moderately persistent	2239348
	FL	02960 SL	9.62 / 301	none	Non-persistent	2239350
	ID	200	45.6 / 224	none	Moderately persistent	2239347
	ON	(Sivanto	99.6 / 281	none	Moderately persistent	2239354
	PEI	200 SL) @	87.8 / 392	none	Moderately persistent	
	SK	1×600 g a.i./ha (nominal)	304 / 4300	none	Persistent	
	Germany	BYI	38.4 / 335	none	Slightly persistent	2239356
	Germany	02960 SL	42.0 / 192	none	Slightly persistent	
	Germany	200	40.8 / 144	none	Slightly persistent	
	UK	(Sivanto	310 / 2040	none	Persistent	
	Italy	200 SL) @	8.3 / 138	none	Non-persistent	
	Spain	1×250 g a.i./ha (nominal)	27.7 / 61.1	none	Slightly persistent	
Biotransformation in aquatic environment						
Property	Test substance	DT <sub>50</sub> /t <sub>1/2-rep</sub> (days)	Major transformation products	Comments/classification	PMRA#	
Biotransformation in aerobic water systems	BYI 02960	Water: 8.5-9.8 / 48.5 – 60.3	DFA up to 6.9%	Persistent in whole system	2239486	
		Whole system 195 – 208.2 / 195 – 208.2				
		Water: 34.5 – 66.2 / 63.6 – 123.8		Persistent in whole system	2239488	
		Whole system 246 – 285 / 246 - 285				
Biotransformation in anaerobic water systems	BYI 02960	Whole system DT <sub>50</sub> : 416 – > 1000	None	Persistent in whole system	2239448	
Biotransformation in aerobic water systems	DFA	Water: 53.1 – 371 / 154 – 371	None	Moderately persistent to persistent in whole system	2239487	
		Whole system 121 – 951 / 121 - 951				
Outdoor Microcosm	BYI	Water: 79.5	NA	Moderately persistent	2239489	



Property	Test substance	DT <sub>50</sub> /t <sub>1/2</sub> - rep (days)	Major transformation products	Comments/classification	PMRA#
Pond	02960	Whole system 91.5			
<b>Partitioning</b>					
Relatively even between water phase and sediment phase					

Table 13 Summary of EECs used for screen level risk assessment

Product	Application method		Maximum seasonal rate (g a.i./ha)	Spray drift (%)	Terrestrial EEC		Aquatic EEC (mg a.i./L)	
					Soil exposure <sup>1</sup> (mg a.i./kg)	Foliar exposure <sup>2</sup> (g a.i./ha)	15 cm water <sup>3</sup>	80 cm water <sup>3</sup>
Sivanto 200 SL	Soil drench		1 × 400	NA	0.18	NA	0.27	0.05
	Foliar	All methods	2 × 200 (7 day interval)	NA	0.18	323	0.27	0.05
		Ground spray		11	0.02	35.5	0.03	0.006
		Early airblast		74	0.13	239	0.20	0.037
		Aerial		26	0.05	84	0.07	0.013
BYI 02960 480 FS	Seed treatment		37.75 (0.068 mg a.i./seed)	NA	0.017	NA	NA	NA

<sup>1</sup> Calculated using a soil half-life of 265 days and by assuming a soil bulk density of 1.5 g/cm<sup>3</sup> and a soil depth of 15 cm.

<sup>2</sup> Calculated using a foliar half-life of 10 days.

<sup>3</sup> Aquatic EECs are calculated by assuming flupyradifurone is stable and is applied direct over spray on water bodies of different depths.

Table 14 Effects of flupyradifurone on terrestrial organisms (excluding bees)

Test organisms	Test substance	Exposure	Endpoints (mg/kg dw soil)	Degree of toxicity	PMRA #
<b>Invertebrates</b>					
earthworm	BYI 02960	14-Day acute	LC <sub>50</sub> : 213.2 mg a.i./kg dw soil NOEC: < 5 mg a.i./kg dw soil		2239274
	Sivanto 200 SL	14-Day acute	LC <sub>50</sub> : 121 mg a.i./kg dw soil (709 mg product/kg dw soil) NOEC: < 100 mg/kg dw soil (17 mg a.i./kg dw soil)		2236644
	Sivanto 200 SL	56-Day chronic	LC <sub>50</sub> : > 89 mg/kg dw soil (> 15 mg a.i./kg dw soil) NOEC: 1.5 mg a.i./kg dw soil (8.9 mg product/kg dw soil)		2239407
	DFA	14-Day acute	LC <sub>50</sub> : > 1000 mg/kg dw soil NOEC: 31.3 mg/kg dw soil		2239279
	DFA	56-Day chronic	LC <sub>50</sub> : > 110 mg/kg dw soil NOEC: 62 mg/kg dw soil		2239406
	6-CNA	14-Day acute (limit test)	LC <sub>50</sub> : > 1000 mg/kg dw soil NOEC: 1000 mg/kg dw soil		2239280
	6-CNA	56-Day chronic	LC <sub>50</sub> : > 95.0 mg/kg dw soil NOEC: 95.0 mg/kg dw soil		2239408
	Sivanto 200 SL	11-month field study	No unacceptable effects on the abundance and biomass of the		2236669



Test organisms	Test substance	Exposure	Endpoints (mg/kg dw soil)	Degree of toxicity	PMRA #
			total earthworm population up to 1500 g a.i./ha		
parasitoid wasp ( <i>Aphidius rhopalosiphii</i> )	Sivanto 200 SL	48h-acute (glass surface)	LR <sub>50</sub> : <0.5 g a.i./ha		2236639
predatory mite ( <i>Typhlodromus pyri</i> )		7d-residue contact (glass surface)	LR <sub>50</sub> : 17 g a.i./ha		2236638
parasitoid wasp ( <i>Aphidius rhopalosiphii</i> )		48h-extended (plant surface)	LR <sub>50</sub> : 2.02 g a.i./ha		2236646
predatory mite ( <i>Typhlodromus pyri</i> )		14d-extended (Leave surface)	LR <sub>50</sub> : 177 g a.i./ha		2236645
ladybird beetle ( <i>Coccinella septempunctata</i> L.)		17d-extended (leave surface)	LR <sub>50</sub> : 273.9 g a.i./ha		2236648
rove beetle ( <i>Aleochara bilineata</i> Gyll.)		Chronic (sandy soil)	ER <sub>50</sub> : > 300 g a.i./ha		2236647
Soil mite ( <i>Hypoaspis aculeifer</i> )		14d-chronic (artificial soil)	NOEC: 170 mg ai/kg dw soil (1000 mg product/kg dw soil)		2239185
Soil mite ( <i>Hypoaspis aculeifer</i> )	DFA	14d-chronic (artificial soil)	NOEC: 1000 mg ai/kg dw soil		2239219
Soil mite ( <i>Hypoaspis aculeifer</i> )	6-CNA	14d-chronic (artificial soil, limit test)	NOEC: 100 mg ai/kg dw soil		2239217
Springtail ( <i>Folsomia candida</i> )	Sivanto 200 SL	28d-chronic (artificial soil)	NOEC: 1.44 mg a.i./kg		2236681
Springtail ( <i>Folsomia candida</i> )	DFA	28d-chronic (artificial soil)	LC <sub>50</sub> : > 100 mg/kg NOEC: 100 mg/kg		2239218
Springtail ( <i>Folsomia candida</i> )	6-CNA	28d-chronic (artificial soil)	LC <sub>50</sub> : > 100 mg/kg NOEC: 90 mg/kg		2239220
Predatory Bug ( <i>Orius laevigatus</i> )	Sivanto 200 SL	Semi-field	no aging: 100% mortality; 14-d aging: 75.6 mortality; 28-d aging: 24.5% mortality, no effect on reproduction; 42-d aging: 9.8% mortality, no effect on reproduction		2236654

Test organisms	Test substance	Exposure	Endpoints (mg/kg dw soil)	Degree of toxicity	PMRA #
parasitoid wasp ( <i>Aphidius rhopalosi-phi</i> )		Semi-field	no aging: 100% mortality; 14-d aging: 90.0% mortality; 28-d aging: 76.7% mortality; 42-d aging: 36.7% mortality; 89.9% reduction in reproduction; 49-d aging: 20.0% mortality, no effect on reproduction 56-d aging: 6.7% mortality, no effect on reproduction		2236653
arthropod fauna - grassland		field	NOER <sup>1</sup> : 5.1 g a.i./ha (population) NOEAER <sup>2</sup> : 21 g a.i./ha (population) <b>NOER: 21 g a.i./ha (community)</b>		2236672
arthropod fauna - grassland		field	<b>NOER<sup>1</sup>: 0.5 g a.i./ha (population)</b> NOEAER <sup>2</sup> : 21 g a.i./ha (population) NOER: 21 g a.i./ha (community)		2236670
<b>Birds</b>					
Northern Bobwhite quail ( <i>Colinus virginianus</i> )	BY1 02960	Acute oral	<b>LD<sub>50</sub>: 232 (173-313) mg a.i./kg bw</b> NOEL: 100 mg a.i./kg bw	Moderately toxic	2239292
Canary ( <i>Serinus canaria</i> )		Acute oral	LD <sub>50</sub> : 330 (215-625) mg a.i./kg bw	Moderately toxic	2239293
chicken ( <i>Gallus gallus domesticus</i> )		Acute oral (Limit test)	LD <sub>50</sub> : >2000 mg a.i./kg bw NOEL: <2000 mg a.i./kg bw	Practically non-toxic	2239294
Northern Bobwhite quail ( <i>Colinus virginianus</i> )		Acute Dietary	LC <sub>50</sub> >4876 mg a.i./kg feed <b>LD<sub>50</sub> &gt;470 mg a.i./kg bw/d</b>	Slightly toxic	2239411
mallard duck ( <i>Anas platyrhyn- chos</i> )		Acute Dietary	LC <sub>50</sub> >4741 mg a.i./kg feed LD <sub>50</sub> >825 mg a.i./kg bw/d	Slightly toxic	2239410
mallard duck ( <i>Anas platyrhyn- chos</i> )		reproduction	NOEC: >845 mg a.i./kg feed NOEL: >83 mg a.i./kg bw/d		2239518
Northern Bobwhite ( <i>Colinus virginianus</i> )	Sivanto 200 SL	reproduction	NOEC: 302 mg a.i./kg feed <b>NOEL: 40 mg a.i./kg bw/d</b>		2239520
Northern Bobwhite quail ( <i>Colinus</i> )		Acute oral	LD <sub>50</sub> : 459 (339 – 616) mg a.i./kg bw NOEL: 250 mg a.i./kg bw	Moderately toxic	2236682
chicken ( <i>Gallus gallus domesticus</i> )		Acute oral (Limit test)	LD <sub>50</sub> : > 2000 mg/kg bw (342 mg a.i./kg bw)	Practically non-toxic	2236683

Mammals					
Rat	BYI 02960	Acute oral	LD <sub>50</sub> : 300 mg/kg bw ♀	Moderately toxic	2239256
		2-generation reproduction (dietary)	NOAEL: 32/39 mg/kg bw/d (500 ppm)		2239237
Vascular plants					
Vascular plant	Sivanto 200 SL	21-d Seedling emergence	ER <sub>25</sub> : >410 g a.i./ha		2239162
		21-d Vegetative vigour	ER <sub>25</sub> : >410 g a.i./ha		2239164

<sup>1</sup>: USEPA classification (1985), where applicable.

<sup>2</sup>: NOEAER: No Observed Ecologically Adverse Effect Rate

**Table 15 Effects of flupyradifurone, Sivanto 200 SL and BYI 02960 480 FS formulations and the transformation products on bees.**

Chemical	Exposure	Endpoint value	Degree of toxicity <sup>1</sup>	Doc. ID. PMRA
BYI 02960 (TGA)	48h-Oral	LD <sub>50</sub> : 1.2 µg a.i./bee	Highly toxic	2239287
	48h-Contact	LD <sub>50</sub> : > 200 µg a.i./bee	Practically non-toxic	
	72h-Contact	LD <sub>50</sub> : > 158.4 µg a.i./bee		
	96h-Contact	LD <sub>50</sub> : > 122.8 µg a.i./bee		
	10d-continuous feeding	NOEC: 10,000 µg a.i./L (0.464 µg a.i./bee/day) No effect at highest concentration		2239264
	21d-in vitro larvae	NOEC: 10,000 µg a.i./kg diet (0.55 µg a.i./larvae/day) No effect at highest concentration		2239265
	Colony feeding study	NOEC: 10,000 µg a.i./kg diet (field spiked sugar, pollen exposure)		2239404
BYI 02960 480 FS (Seed treatment product)	48h-Oral	LD <sub>50</sub> : 3.4 µg a.i./bee	Moderately toxic	2236542
	48h-Contact	LD <sub>50</sub> : 137.3 µg a.i./bee		
	72h-Contact	LD <sub>50</sub> : 82.3 µg a.i./bee	Practically non-toxic	
	96h-Contact	LD <sub>50</sub> : 68.6 µg a.i./bee		
Sivanto 200 SL (Foliar and soil drench product)	48h-Oral	LD <sub>50</sub> : 3.2 µg a.i./bee	Moderately toxic	2236691
	48h-Contact 72h-Contact	LD <sub>50</sub> : 17.1 µg a.i./bee LD <sub>50</sub> : 15.7 µg a.i./bee	Practically non-toxic	

Chemical	Exposure	Endpoint value	Degree of toxicity <sup>1</sup>	Doc. ID. PMRA
Sivanto 200 SL (17.1% a.i.) + tebuconazole EW 250C G (17.0% a.i.)	48h-Oral	LD <sub>50</sub> : 0.2 µg a.i./bee	Highly toxic	2236693
	72h-Contact	LD <sub>50</sub> : 1 µg a.i./bee		
Transformation Products difluoroethyl-amino-furanone <sup>2</sup> hydroxy Difluoroacetic acid 6-chloronicotinic acid 6-chloro-picolyalcohol	48h-Oral	LD <sub>50</sub> : > 100 µg a.i./bee	Practically non-toxic	2239281
	48h-Contact	LD <sub>50</sub> : > 100 µg a.i./bee		2239288
	10d-continuous feeding	NOEC: 10,000 µg a.i./L		2239284 2239282 2239285
				2239262 2239263 2239266 2239259 2239260
<sup>1</sup> Atkins et al. 1981				
<sup>2</sup> Oral LD <sub>50</sub> : > 81.5 µg a.i./be				

Table 16 Effects of flupyradifurone on aquatic organisms

Test substance	Test species	Exposure	Endpoints	Degree of toxicity <sup>a</sup>	PMRA #
<b>Freshwater invertebrates</b>					
Flupyradifurone TGA1	<i>Daphnia magna</i>	48h-Acute (static, limit test)	EC <sub>50</sub> : >77.6 mg/L NOEC: 77.6 mg/L	Slightly toxic <sup>b</sup>	2239605
DFA (Na-salt)	<i>Daphnia magna</i>	48h-Acute (static, limit test)	EC <sub>50</sub> : >10.2 mg a.i./L NOEC: 10.2 mg a.i./L	Slightly toxic <sup>b</sup>	2239607
6-CNA	<i>Daphnia magna</i>	48h-Acute (semi-static)	EC <sub>50</sub> : >95.1 mg/L NOEC: 95.1 mg/L	Slightly toxic	2239606
Flupyradifurone TGA1	<i>Daphnia magna</i>	21d-Chronic (Static renewal)	NOEC: 3.42 mg a.i./L		2239598
BYI 02960-succinamide	<i>Daphnia magna</i>	21d-Chronic (Static renewal)	LOEC: 106 mg a.i./L NOEC: 46.3 mg/L		2239604
Sivanto 200 SL	<i>Daphnia magna</i>	48h-Acute (static)	EC <sub>50</sub> : 115 mg a.i./L	Practically non-toxic	2236701



Test substance	Test species	Exposure	Endpoints	Degree of toxicity <sup>a</sup>	PMRA #
Flupyradifurone TGAI	Midge larvae ( <i>Chironomus riparius</i> )	48h-Acute (static)	EC <sub>50</sub> : 63.9 µg a.i./L	Slightly toxic	2239290
BYI 02960- succinamide	Midge larvae ( <i>Chironomus riparius</i> )	48h-Acute (static)	EC <sub>50</sub> > 104.5 mg/L NOEC: 74.4 mg/L	Slightly toxic	2239612
BYI 02960- azabicyclo- succinamide	Midge larvae ( <i>Chironomus riparius</i> )	48h-Acute (static)	EC <sub>50</sub> > 114.5 mg/L NOEC: 82.0 mg/L	Slightly toxic	2239613
6-CNA	Midge larvae ( <i>Chironomus tentans</i> )	96h-Acute (static renewal, limit test)	EC <sub>50</sub> > 1 mg/L NOEC: 1 mg/L	Moderately toxic <sup>b</sup>	2239611
Flupyradifurone TGAI	Midge ( <i>Chironomus riparius</i> )	28d-chronic (spiked water- sediment)	<b>NOEC: 10.5 µg a.i./L</b>		2239409
Sivanto 200 SL	Midge ( <i>Chironomus riparius</i> )	28d-chronic (static spiked water- sediment)	NOEC: 12 µg a.i./L		2236700
DFA (Na-salt)	Midge ( <i>Chironomus riparius</i> )	28d-chronic (static water- sediment, limit test)	NOEC: 105 mg/L		2239609
6-CNA	Midge ( <i>Chironomus riparius</i> )	28d-chronic (static water- sediment, limit test)	NOEC: 102 mg/L		2239610
<b>Freshwater green algae</b>					
Flupyradifurone TGAI	Green Alga ( <i>Pseudokirchneriella subcapitata</i> )	96h-Acute (static)	E <sub>r</sub> C <sub>50</sub> : > 80 mg a.i./L NOE <sub>r</sub> C: 80 mg a.i./L		2239076
Sivanto 200 SL	Green Alga ( <i>Pseudokirchneriella subcapitata</i> )	72h-Acute (static)	E <sub>r</sub> C <sub>50</sub> : > 42.8 mg a.i./L NOE <sub>r</sub> C: 42.8 mg a.i./L		2230702
6-CNA	Green Alga ( <i>Pseudokirchneriella subcapitata</i> )	72h-Acute (static)	E <sub>r</sub> C <sub>50</sub> : > 100 mg/L NOE <sub>r</sub> C: 100 mg/L		2239080
BYI 02960- succinamide	Green Alga ( <i>Pseudokirchneriella subcapitata</i> )	72h-Acute (static, limit test)	E <sub>r</sub> C <sub>50</sub> : > 11.4 mg/L NOE <sub>r</sub> C: 11.4 mg/L		2239078
DFA (Na-salt)	Green Alga ( <i>Pseudokirchneriella subcapitata</i> )	72h-Acute (static, limit test)	E <sub>r</sub> C <sub>50</sub> : > 10.2 mg/L NOE <sub>r</sub> C: 10.2 mg/L		2239077
<b>Freshwater fish</b>					
Flupyradifurone TGAI	Rainbow Trout ( <i>Oncorhynchus mykiss</i> )	96h-acute (static)	LC <sub>50</sub> : > 74.2 mg a.i./L NOEC: 74.2 mg a.i./L	Slightly toxic <sup>b</sup>	2239595
	Fathead Minnow ( <i>Pimephales promelas</i> )	96h-acute (static)	LC <sub>50</sub> : > 70.5 mg a.i./L NOEC: 70.5 mg a.i./L	Slightly toxic <sup>b</sup>	2239614

Test substance	Test species	Exposure	Endpoints	Degree of toxicity <sup>a</sup>	PMRA #
	common carp ( <i>Cyprinus carpio</i> )	96h-acute (static, limit test)	LC <sub>50</sub> : >80 mg a.i./L NOEC: 80 mg a.i./L	Slightly toxic <sup>b</sup>	2239615
Sivanto 200 SL	Rainbow Trout ( <i>Oncorhynchus mykiss</i> )	96h-acute (static, limit test)	LC <sub>50</sub> : >100 mg a.i./L NOEC: <100 mg a.i./L	Practically non-toxic <sup>b</sup>	2236693
	common carp ( <i>Cyprinus carpio</i> )	96h-acute (static, limit test)	LC <sub>50</sub> : >100 mg a.i./L NOEC: 100 mg a.i./L	Practically non-toxic <sup>b</sup>	2236694
BYI 02960-succinamide	Rainbow Trout ( <i>Oncorhynchus mykiss</i> )	96h-acute (static, limit test)	LC <sub>50</sub> : >114 mg/L NOEC: 114 mg/L	Practically non-toxic <sup>b</sup>	2239617
DFA (Na-salt)	Rainbow Trout ( <i>Oncorhynchus mykiss</i> )	96h-acute (static, limit test)	LC <sub>50</sub> : >10.35 mg/L NOEC: 10.35 mg/L	Slightly toxic <sup>b</sup>	2239616
Flupyradifurone TGA1	Fathead Minnow ( <i>Pimephales promelas</i> )	ELS (flow-through)	NOEC: 4.41 mg a.i./L		2239516
<b>Amphibian</b>					
Flupyradifurone TGA1	African clawed frog tadpole ( <i>Xenopus laevis</i> )	48h-acute (static, limit test)	LC <sub>50</sub> : >74.2 mg a.i./L NOEC: 74.2 mg a.i./L		2239596
<b>Freshwater Vascular plants</b>					
Flupyradifurone TGA1	Duckweed ( <i>Lemna gibba</i> )	7d-acute (static-semi-renewal)	EC <sub>50</sub> : >67.7 mg a.i./L NOEC: 34.2 mg a.i./L		2239096
<b>Marine organisms</b>					
Flupyradifurone TGA1	sheepshead minnows ( <i>Cyprinodon variegatus</i> )	96h-acute (static)	LC <sub>50</sub> : >83.9 mg a.i./L NOEC: 83.9 mg a.i./L	Slightly toxic <sup>b</sup>	2239268
	Eastern oyster ( <i>Crassostrea virginica</i> )	96h-acute (static, limit test)	LC <sub>50</sub> : >29 mg a.i./L NOEC: 29 mg a.i./L	Slightly toxic <sup>b</sup>	2239269
	mysid shrimp ( <i>Americamysis bahia</i> )	96h-acute (static)	LC <sub>50</sub> : 0.25 mg a.i./L NOEC: 0.12 mg a.i./L	Highly toxic	2239270
		28d- Life cycle (flow-through)	NOEC: 13.2 µg a.i./L		2236271

<sup>a</sup> USEPA classification, where applicable<sup>b</sup> toxicity endpoints were based on the highest concentration tested.**Table 17 Risk to soil dwelling organisms as a result of direct in-field and off-field exposure**

Organism	Exposure	Endpoint value	EEC	RQ	LOC exceeded?	Risk
Earthworm	Acute	LC <sub>50</sub> : 121 mg a.i./kg dw soil	0.18 mg a.i./kg soil	<0.01	No	Negligible risk
	Chronic	NOEC: 1.5 mg a.i./kg dw soil	0.18 mg a.i./kg soil	0.12	No	Negligible risk
Soil-dwelling arthropods	Chronic	ER <sub>50</sub> : > 300 g a.i./ha	Direct application: 400 g a.i./ha	<1.33	Yes	Risk with uncertainty

Organism	Exposure	Endpoint value	EEC	RQ	LOC exceeded?	Risk
			field spray (11%): 44 g a.i./ha	0.15	No	Negligible risk
			Early airblast (74%): 296 g a.i./ha	0.99	No	Negligible risk
			Aerial (26%): 104 g a.i./ha	0.35	No	Negligible risk

**Table 18 Risk assessment to foliar-dwelling organisms as a result of in-field and off-field exposure**

Exposure	Endpoint	EEC	Risk quotient	LOC exceeded?
48h-exposure (glass surface) <i>A. rhopalosiphi</i>	LR <sub>50</sub> < 0.5 g a.i./ha	<b>In-field:</b> 323 g a.i./ha  <b>Off-field</b> Field spray (11% drift): 35.5 g a.i./ha Early airblast (74% drift): 239 g a.i./ha Aerial (26% drift): 84 g a.i./ha	> 646  > 71 > 478 > 168	Yes  Yes Yes Yes
7d-exposure (glass surface) <i>T. pyri</i>	LR <sub>50</sub> : 17 g a.i./ha	<b>In-field:</b> 323 g a.i./ha  <b>Off-field</b> Field spray (11% drift): 35.5 g a.i./ha Early airblast (74% drift): 239 g a.i./ha Aerial (26% drift): 84 g a.i./ha	19  2.1 14.1 4.95	Yes  Yes Yes Yes
48h-Extended (leaf surface) <i>A. rhopalosiphi</i>	LR <sub>50</sub> : 2.02 g a.i./ha	<b>In-field:</b> 323 g a.i./ha  <b>Off-field</b> Field spray (11% drift): 35.5 g a.i./ha Early airblast (74% drift): 239 g a.i./ha Aerial (26% drift): 84 g a.i./ha	160  17.6 118 41.6	Yes  Yes Yes Yes
14d-Extended (leaf surface) <i>T. pyri</i>	LR <sub>50</sub> : 177 g a.i./ha	<b>In-field:</b> 323 g a.i./ha  <b>Off-field</b> Field spray (11% drift): 35.5 g a.i./ha Early airblast (74% drift): 239 g a.i./ha Aerial (26% drift): 84 g a.i./ha	1.82  0.20 1.35 0.48	Yes  No Yes No
17-d Extended (leaf surface) <i>Coccinella septempunctata</i>	LR <sub>50</sub> : 273.9 g a.i./ha	<b>In-field:</b> 323 g a.i./ha  <b>Off-field</b> Field spray (11% drift): 35.5 g a.i./ha Early airblast (74% drift): 239 g a.i./ha Aerial (26% drift): 84 g a.i./ha	1.18  0.13 0.87 0.31	Yes  No No No

Exposure	Endpoint	EEC	Risk quotient	LOC exceeded?
28-d Extended (sandy soil) <i>Aleochara bilineata</i>	ER <sub>50</sub> (reproduction) > 300 g a.i./ha	<b>In-field:</b> 323 g a.i./ha  <b>Off-field</b> Field spray (11% drift): 35.5 g a.i./ha Early airblast (74% drift): 239 g a.i./ha Aerial (26% drift): 84 g a.i./ha	< 1.08  0.12 0.80 0.28	Yes  No No No

**Table 19 Refinement to the risk to foliar-dwelling and soil-dwelling organisms from in-field and off-field exposure.**

Exposure	Endpoint	Refined EEC	Risk quotient	LOC exceeded?
<b>Tier II in-field exposure</b>				
48-h Extended (leaf surface) <i>A. rhopalosiphi</i>	LR <sub>50</sub> : 2.02 g a.i./ha	96.9 g a.i./ha (30% foliar deposition factor) 161.5 g a.i./ha (50% foliar deposition factor) 226.1 g a.i./ha (70% foliar deposition factor)	<b>48.0</b> <b>80.0</b> <b>112</b>	<b>Yes</b> <b>Yes</b> <b>Yes</b>
14-d Extended (leaf surface) <i>T. pyri</i>	LR <sub>50</sub> : 177 g a.i./ha	96.9 g a.i./ha (30% foliar deposition factor) 161.5 g a.i./ha (50% foliar deposition factor) 226.1 g a.i./ha (70% foliar deposition factor)	0.55 0.91 <b>1.28</b>	No No <b>Yes</b>
17-d Extended (leaf surface) <i>Coccinella septempunctata</i>	LR <sub>50</sub> : 273.9 g a.i./ha	96.9 g a.i./ha (30% foliar deposition factor) 161.5 g a.i./ha (50% foliar deposition factor) 226.1 g a.i./ha (70% foliar deposition factor)	0.35 0.59 0.83	No No No
28-d Extended (sandy soil) <i>Aleochara bilineata</i>	ER <sub>50</sub> (reproduction) > 300 g a.i./ha	226.1 g a.i./ha (70% soil deposition factor) 161.5 g a.i./ha (50% soil deposition factor) 96.9 g a.i./ha (30% soil deposition factor)	0.65 0.54 0.32	No No No
<b>Tier II off-field exposure</b>				
48-h Extended (leaf surface) <i>A. rhopalosiphi</i>	LR <sub>50</sub> : 2.02 g a.i./ha	Field spray (11% drift): 3.55 g a.i./ha Early airblast (74% drift): 23.9 g a.i./ha Aerial (26% drift): 8.4 g a.i./ha	<b>1.76</b> <b>11.8</b> <b>4.16</b>	Yes Yes Yes
14-d Extended (leaf surface) <i>T. pyri</i>	LR <sub>50</sub> : 177 g a.i./ha	Early airblast (74% drift): 23.9 g a.i./ha	0.135	No

**Table 20 Details of results from the semi-field and field studies**

Study type	Exposure and endpoints
Aged residues Predatory Bug ( <i>O. laevigatus</i> )	<b>Application rate: 2 × 250 a.i./ha (10-day interval)</b> After 2 <sup>nd</sup> application (no aging): 100% mortality; 14-day aging: 75.6% corrected mortality; 28-day aging: 24.5% corrected mortality and no effect on reproduction observed; 42-day aging: 9.8% corrected mortality and no effect on reproduction observed.



Study type	Exposure and endpoints
Semi-field Parasitoid wasp ( <i>A. rhopalosiphi</i> )	<b>Application rate: <math>2 \times 250</math> a.i./ha (10-day interval)</b> After 2 <sup>nd</sup> application (no aging): 100% mortality; 14-day aging: 90.0% corrected mortality; 28-day aging: 76.7% corrected mortality, reproduction not tested; 42-day aging: 36.7% corrected mortality and 89.9% reduction in reproduction; 49-day aging: 20.0% corrected mortality and no effect on reproduction observed; 56-day aging: 6.7% corrected mortality and no effect on reproduction observed.
Field study Arthropod fauna – grassland (PMRA# 2236672)	<b>Application rates: 0.51, 1.7, 5.1, and 21 a.i./ha (equivalent to typical drift values for different use patterns of the test item)</b> NOER (community level): 21 g a.i./ha NOER (population level): 5.1 g a.i./ha NOEAER (population level): 21 g a.i./ha
Field study Arthropod fauna – grassland (PMRA# 2236670)	<b>Application rates: 0.51, 1.7, 5.1, and 21 a.i./ha (equivalent to typical drift values for different use patterns of the test item)</b> NOER (community level): 21 g a.i./ha NOER (population level): 0.51 g a.i./ha NOEAER (population level): 21 g a.i./ha Only 3 taxa were adversely affected. They all recovered within the ecologically acceptable time frame of two months.

**Table 21 Screening Level EECs and RQ values for honeybees based on foliar, drench, and seed treatment applications.**

Application Rate	Life-Stage	Exposure Route	Exposure Estimate <sup>1</sup>	Acute RQ	Chronic RQ
Foliar Applications					
200 g a.i./ha	Adults	Contact	0.48 µg a.i./bee	0.03 <sup>2</sup>	ND
		Diet	5.8 µg a.i./bee	4.8 <sup>3</sup>	12.5 <sup>4</sup>
	Brood	Diet	2.4 µg a.i./bee	ND	4.4 <sup>5</sup>
Soil Drench					
400 g a.i./ha	Adults	Diet	0.026 µg a.i./bee	0.02 <sup>3</sup>	0.06 <sup>4</sup>
	Brood		0.01 µg a.i./bee	ND	0.02 <sup>5</sup>
Seed Treatments					
37.75 g a.i./ha	Adults	Diet	0.29 µg a.i./bee	0.24 <sup>3</sup>	0.6 <sup>4</sup>
	Brood		0.124µg a.i./bee	ND	0.2 <sup>5</sup>

ND = No Data Available

<sup>1</sup> Based on food consumption rates for larvae (0.124 g/day) and adult (0.292 g/day) worker bees and concentration in pollen and nectar

<sup>2</sup> LD<sub>50</sub> = 15.7 µg ai/bee based on acute contact toxicity data for SL 200 G formulation

<sup>3</sup> LD<sub>50</sub> = 1.2 µg ai/bee based on acute oral toxicity data for TGA1

<sup>4</sup> 10-d NOEC = 0.464 µg ai/bee/day for adult worker bees

<sup>5</sup> 21-d NOEC = 0.55 µg ai/larvae/day for bee larvae

**Bold** values indicate that acute (RQ ≥ 0.4) and/or chronic (RQ ≥ 1) LOCs are exceeded

**Table 22 Risk to different castes of bees based on maximum residues of flupyradifurone (mg a.i./kg) in various matrices following soil drench and foliar applications to different crops.**

PMRA No.	Crop	Number of Applications (g a.i./ha)	Application Type	Matrix	Maximum Residue (mg/kg)	Worker Bee Acute RQ	Nurse Bee Acute RQ	Worker Bee Chronic RQ	Bee Larvae Chronic RQ
2236658	Tomato	1 at 200	Drench	Pollen	0.107	0.08	0.04	0.2	0.07
				Flower <sup>1</sup>	0.315				
2236656	Watermelon	1 at 200	Drench	Pollen	0.002	0.0002	0.0001	0.0006	0.0002
				Nectar	0.001				
				Flowers	0.017				
2236661	Watermelon	3 at 150	Drench	Pollen	0.006	0.0002	0.0002	0.0006	0.0002
				Nectar	0.001				
				Flowers	1.56				
2236659	Citrus	2 at 205	Foliar	Pollen, Traps	1.8	0.05	0.04	0.13	0.06
				Nectar	0.2				
				Blossoms	2				
2236659	Citrus	1 at 410	Foliar	Pollen, Traps	1.1	0.08	0.05	0.2	0.07
				Nectar	0.31				
				Blossoms	5.1				
2236660	Melon	1 at 410	Drench	Pollen	0.5	0.2	0.09	0.5	0.2
				Nectar	0.76				
				Blossoms	0.38				
2236660	Melon	2 at 205	Foliar	Pollen	1.5	0.09	0.05	0.2	0.09
				Nectar	0.36				
				Blossoms	2.8				
2236662	Cotton	2 at 205	Foliar	Pollen	0.432	5.3	2.6	13.7	4.8
				Nectar, Total	21.83				
				Nectar, Floral	0.386				
				Nectar, inner-bracteal	12.2				
				Nectar, sub-bracteal	15.9				
				Nectar, pink floral	0.311				
				Blossoms	12.1				
2236664	Blueberry	2 at 404 <sup>1</sup>	Foliar	Pollen	67.6	0.2	0.6	0.4	0.6
				Nectar	0.64				
				Blossoms	6.49				
2236666	Apple	2 at 205	Foliar	Pollen (Highest Trial Max)	26.2	0.3	0.3	0.8	0.4
				Nectar (Highest Trial Max)	1.2				
				Blossoms (Highest Trial Max)	27.7				
				Pollen	8.3				

PMRA No.	Crop	Number of Applications (g a.i./ha)	Application Type	Matrix	Maximum Residue (mg/kg)	Worker Bee Acute RQ	Nurse Bee Acute RQ	Worker Bee Chronic RQ	Bee Larvae Chronic RQ
2236665	Apple	2 at 205	Foliar	(Lowest Trial Max)		0.4	0.5	0.9	0.6
				Nectar (Lowest Trial Max)	0.3				
				Blossoms (Lowest Trial Max)	20.1				
				Pollen, Legs	39				
				Nectar	1.5				
				Blossoms	113				

**Bold** values indicate that acute ( $RQ \geq 0.4$ ) and/or chronic ( $RQ \geq 1$ ) LOCs are exceeded

EECs were calculated for worker bees based on a nectar consumption rate of 0.292 g/day.

EECs were calculated for nurse bees based on a combination of pollen and nectar consumption rates of 0.0096 and 0.140 g/day, respectively.

EECs were calculated for larval bees based on a combination of pollen and nectar consumption rates of 0.0036 and 0.120 g/day, respectively.

$LD_{50} = 1.2 \mu\text{g ai/bee}$  based on acute oral toxicity data for TGA1

10-d NOEC = 0.464  $\mu\text{g ai/bee/day}$  for adult worker bees

21-d NOEC = 0.55  $\mu\text{g ai/larvae/day}$  for bee larvae

<sup>1</sup> Used as a surrogate for concentration in nectar

<sup>2</sup> Twice the proposed application rate was accidentally used in this study; therefore residues are likely to be overestimated.

**Table 23 Tier II and III Semi-field Colony-Level Bee Toxicity Studies**

Study	Application Rate (g a.i./ha and timing)	Adult Mortality	Adult Foraging	Brood Development	Comments
Tier II					
Rentschler (2012)  PMRA 2236686	Pre-flowering foliar application at 200 g a.i./ha 6 d before hive setup to <i>P. tanacetifolia</i> , followed by 200 g a.i./ha application 4 d after hive setup during flowering while bees were foraging.	Increased for 1 day following second application relative to control.	Mean number of forager bees/m <sup>2</sup> was reduced following second application for two days relative to the control.	No substantial effects were observed on colony strength, brood development (sum of cells containing eggs, larvae and pupae) or development of the food storage area (sum of cells containing nectar and pollen) following the second application.	Colonies remained in tunnels for prolonged period (16 days).  Residues were measured in flowers, and comb nectar and pollen.

Proebsting (2012)  PMRA 2236685	Soil application at 300 g a.i./ha before planting <i>P. tanacetifolia</i> seeds followed by pre-flowering foliar application at 200 g a.i./ha 14 d before hive setup, followed by 200 g a.i./ha application 4 d after hive setup during flowering while bees were foraging.	No clear increase relative to control	Decreased on day following 2 <sup>nd</sup> foliar application then returned to control levels.	Unfavourable weather conditions prior to hive set up, followed by confined conditions in the tunnels led to uniform decreases in mean abundance of brood cells for the control, treatment and toxic reference hives and also (indirectly) contributed to the colonies having no pollen stores.	The colony size at set-up was 7000-13,800 bees. Upper range is large for a tunnel study. Consistently high mortality in control hives confounds assessment of treatment effects. Difficulty determining whether mortality in the treatment group was attributed to effects of the treatment or limitations of the food supply. Soil application (300 g a.i./ha) is below proposed rate in Canada (400g a.i./ha).
Proebsting (2012)  PMRA 2236684	Soil application at 300 g a.i./ha before planting <i>P. tanacetifolia</i> seeds followed by pre-flowering foliar application at 200 g a.i./ha 4 d before hive setup, followed by 200 g a.i./ha application 3 d after hive setup during flowering while bees were foraging.	Possibly increased for up to 7 days following third application during flowering while bees were foraging then returned to control levels. High variability makes interpretation difficult.	Slight reduction in foraging on the day of the 3 <sup>rd</sup> test item application, after the treatment, as well as on day 1 following application and from day 3 to 5 following application.	No significant effects were noted on brood and food development.	Results are confounded by the large disparity in colony size between the control and treatment groups at the beginning of the study.  The soil application rate used (300 g a.i./ha) was below the maximum single application rate proposed for Canada (400 g a.i./ha).  Residues were measured in soil, flowers, and comb nectar and pollen.



Schnorbach (2012)  PMRA 2236687	Foliar applications at rates of 75 and 150 g a.i./ha to flowering <i>P. tanacetifolia</i> while bees were actively foraging.	No increase relative to control.	Foraging activity was slightly reduced immediately after treatment at 150 g a.i./ha compared to the control, but recovered fully within a couple of hours.	No distinct differences were found when comparing the extent of nectar- and pollen stores, egg laying activity, larval and pupal abundance, colony strength, hive weight development and overall hive vitality in the test item treatment groups with control performance at any point in time after application.	Application rates used in this study (75 and 150 g a.i./ha) are below many proposed foliar application rates in Canada (200 g a.i./ha).  Residues were not measured in various matrices (flowers, nectar, and pollen) to confirm exposure.
Schnorbach (2012)  PMRA 2236688	Foliar application at a rate of 150 g a.i./ha to flowering <i>P. tanacetifolia</i> while bees were actively foraging 2 days after introduction of colonies to tunnel. Colonies were relocated to a monitoring site on day 13.	No increase relative to control.	No reduction in treatment groups relative to control.	No distinct differences were found when comparing the extent of nectar- and pollen stores, egg laying activity, larval and pupal abundance, colony strength, hive weight development and overall hive vitality in the test item treatment group with control performance at any point in time after application.	The application rate used in this study (150 g a.i./ha) is below many proposed foliar application rates in Canada (200 g a.i./ha).  Residues were not measured in various matrices (flowers, nectar, and pollen) to confirm exposure.
Rentschler (2012)  PMRA 2236689	Pre-flowering foliar application at 200 g a.i./ha 5 d before hive setup to <i>P. tanacetifolia</i> , followed by 200 g a.i./ha application 5 d after hive setup during flowering while bees were foraging.	No increase relative to control.	A reduced flight intensity was observed on the day of the 2 <sup>nd</sup> test item application as well as on some further days during the confined exposure period.	As quantitatively assessed via digital image analysis of individual cells, the tested application scenario did not result in detectable adverse effects on the survival of marked eggs (brood termination rate), on brood development from eggs into adult bees (brood index) as well as on the brood compensation ability (brood compensation index).	Residue samples were only collected in the treatment group at the end of the study when residues would have been diluted by pollen/nectar from other floral sources.  Residue analysis should have also been conducted in the control to determine if contamination had occurred.

Nikolakis <i>et al.</i> (2012)  PMRA 2239404	Bee colonies were exposed under confined conditions in gauze tunnels by <i>ad libitum</i> feeding on treatment-specific sugar- and pollen diet for a period of 6 consecutive weeks during springtime/early summer to nominal 600, 2500 and 10000 µg a.i./kg diet. Colonies were released from confinement to be monitored under field conditions for the remainder of the season until overwintering, and were assessed for a final time after overwintering in the next spring.			Highest exposure (10,000 µg a.i./kg diet) did not result in adverse acute, short-term and long-term effects on mortality, colony strength and -development, brood development, food storage, honey bee behaviour, queen survival, overall hive vitality and colony health, as well as on overwintering performance.	No residues of flupyradifurone were found in any of the control diets. Also no detectable residues of neonicotinoid-agrochemicals as well as no detectable residues of other agrochemicals were found in the bee-collected, natural polyfloral pollen, employed for the preparation of the pollen diet.
Tier III					
Rexer (2012)  PMRA 2236673	Fall 2010 soil application at 310 g a.i./ha before planting oil seed rape treated seeds followed by a spring pre-flowering foliar application at 204 g a.i./ha 6 days after colony setup, followed by 205 g a.i./ha application during flowering while bees were foraging. Colonies were observed to the spring of 2012 to observe treatment effect on overwintering.	Possibly increased for 3 days following third application during flowering while bees were foraging then returned to control levels. High variability makes interpretation difficult.	No clear difference relative to control.  Intensive grooming behaviour and coordination problems in a small fraction of bees in the flupyradifurone treatment group observed following the last foliar application during flowering.	No clear differences were observed relative to the control on colony development (including colony strength, colony health, brood- and food development, weight development of the colonies) as well as on overall colony vitality throughout the entire field exposure period and throughout the entire monitoring period until the end of overwintering in spring 2012.	The percentage of oil seed rape pollen collected per hive was < 1 – 70% in the control field and 18 – 70% in the treatment field. Obviously the bees were foraging on alternate food sources which could influence the results of the study and introduces some uncertainty into the conclusions regarding the treatment effects.  Residues were measured in flowers, pollen combs, bee bread, forager bees, nectar combs, honey, forager bees, beeswax combs and soil.

Rexer (2012)  PMRA 2236675	Fall 2010 soil application at 310.5 g a.i./ha before planting oil seed rape treated seeds followed by a spring pre-flowering foliar application at 208 g a.i./ha 1 day after colony setup, followed by 212 g a.i./ha application during flowering while bees were foraging. Colonies were observed to the spring of 2012 to observe treatment effect on overwintering.	No clear difference relative to control. High variability makes interpretation difficult.	No clear difference relative to control. High variability makes interpretation difficult.	No clear differences were observed relative to the control on colony development (including colony strength, colony health, brood development and food storage, colony weight) as well as on overall colony vitality throughout the entire field exposure period and throughout the entire monitoring period, until the end of overwintering in spring 2012.	The percentage of oil seed rape pollen collected per hive was 13 – 48% in the control field and 28 – 69% in the treatment field. Obviously the bees were foraging on alternate food sources which could influence the results of the study and introduces some uncertainty into the conclusions regarding the treatment effects.  Residues were measured in flowers, pollen combs, forager bees, nectar combs, forager bees, beewax combs and soil.
-------------------------------------	--	---	---	--	---

**Table 24 Risk to birds and mammals as a result of direct on-field and off-field exposure after a single soil application of 400 g a.i./ha**

	Toxicity (mg ai/kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field (74%)		On-field		Off Field (74%)	
			EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ
Small Bird (0.02 kg)										
Acute	23.20	Insectivore	32.56	1.40	24.09	1.04	22.48	0.97	16.64	0.72
	23.20	Granivore (grain and seeds)	5.04	0.22	3.73	0.16	2.40	0.10	1.78	0.08
Dietary	47.00	Insectivore	32.56	0.69	24.09	0.51	22.48	0.48	16.64	0.35
Reproduction	40.00	Insectivore	32.56	0.81	24.09	0.60	22.48	0.56	16.64	0.42
	40.00	Granivore (grain and seeds)	5.04	0.13	3.73	0.09	2.40	0.06	1.78	0.04
Medium Sized Bird (0.1 kg)										
Acute	23.20	Insectivore	25.41	1.10	18.80	0.81	17.54	0.76	12.98	0.56
	23.20	Granivore (grain and seeds)	3.93	0.17	2.91	0.13	1.88	0.08	1.39	0.06
Dietary	47.00	Insectivore	25.41	0.54	18.80	0.40	17.54	0.37	12.98	0.28
	47.00	Granivore (grain and seeds)	3.93	0.08	2.91	0.06	1.88	0.04	1.39	0.03
Reproduction	40.00	Insectivore	25.41	0.64	18.80	0.47	17.54	0.44	12.98	0.32
	40.00	Granivore (grain and seeds)	3.93	0.10	2.91	0.07	1.88	0.05	1.39	0.03

	Toxicity (mg ai/kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field (74%)		On-field		Off Field (74%)	
			EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ
Large Sized Bird (1 kg)										
Acute	23.20	Insectivore	7.42	0.32	5.49	0.24	5.12	0.22	3.79	0.16
	23.20	Granivore (grain and seeds)	1.15	0.05	0.85	0.04	5.12	0.22	0.41	0.02
Dietary	47.00	Insectivore	7.42	0.16	5.49	0.12	5.12	0.11	3.79	0.08
	47.00	Granivore (grain and seeds)	1.15	0.02	0.85	0.02	5.12	0.11	0.41	0.01
Reproduction	40.00	Insectivore	7.42	0.19	5.49	0.14	5.12	0.13	3.79	0.09
	40.00	Granivore (grain and seeds)	1.15	0.03	0.85	0.02	5.12	0.13	0.41	0.01
Small Sized Mammal (0.015 kg)										
Acute	30.00	Insectivore	18.73	0.62	13.86	0.46	12.93	0.43	9.57	0.32
	30.00	Granivore (grain and seeds)	2.90	0.010	2.14	0.072	1.38	0.046	1.02	0.034
Reproduction	7.8	Insectivore	18.73	<b>2.40</b>	13.86	<b>1.78</b>	12.93	<b>1.66</b>	9.57	<b>1.23</b>
	7.8	Granivore (grain and seeds)	2.90	0.37	2.14	0.28	1.38	0.18	1.02	0.13
Medium Sized Mammal (0.035 kg)										
Acute	30.00	Insectivore	16.42	0.55	12.15	0.40	11.33	0.38	8.39	0.28
	30.00	Granivore (grain and seeds)	2.54	0.08	1.88	0.06	1.21	0.04	0.90	0.03
Reproduction	7.8	Insectivore	16.42	<b>2.10</b>	12.15	<b>1.56</b>	11.33	<b>1.45</b>	8.39	<b>1.08</b>
	7.8	Granivore (grain and seeds)	2.54	0.33	1.88	0.24	1.21	0.16	0.90	0.12
Large Sized Mammal (1 kg)										
Acute	30.00	Insectivore	8.77	0.29	6.49	0.22	6.06	0.20	4.48	0.15
	30.00	Granivore (grain and seeds)	1.36	0.05	1.00	0.03	0.65	0.02	0.48	0.02
Reproduction	7.8	Insectivore	8.77	<b>1.12</b>	6.49	0.83	6.06	0.78	4.48	0.57
	7.8	Granivore (grain and seeds)	1.36	0.17	1.00	0.13	0.65	0.08	0.48	0.06

<sup>a</sup> EDE = Estimated daily exposure; is calculated using the following formula: (FIR/BW) × EEC. Where FIR is Food Ingestion Rates (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:

Passerine Equation (body weight < or =200 g):  $FIR (g \text{ dry weight/day}) = 0.398(BW \text{ in g})^{0.850}$

All birds Equation (body weight > 200 g):  $FIR (g \text{ dry weight/day}) = 0.648(BW \text{ in g})^{0.651}$

For mammals, the "all mammals" equation was used:  $FIR (g \text{ dry weight/day}) = 0.235(BW \text{ in g})^{0.822}$

At the screening level, food items representing the most conservative EEC for each size guild are used.



**Table 25 Risk to birds and mammals as a result of direct on-field and off-field exposure after foliar application at  $2 \times 200$  g a.i./ha with a 7-day interval**

	Toxicity (mg ai/kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field (74%)		On-field		Off Field (74%)	
			EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ
Small Bird (0.02 kg)										
Acute	23.20	Insectivore	26.30	1.13	19.46	0.84	18.16	0.78	13.44	0.58
	23.20	Granivore (grain and seeds)	4.07	0.18	3.01	0.13	1.94	0.08	1.44	0.06
	23.20	Frugivore (fruit)	8.14	0.35	6.02	0.26	3.88	0.17	2.87	0.12
Dietary	47.00	Insectivore	26.30	0.56	19.46	0.41	18.16	0.39	13.44	0.29
	47.00	Granivore (grain and seeds)	4.07	0.09	3.01	0.06	1.94	0.04	1.44	0.03
	47.00	Frugivore (fruit)	8.14	0.17	6.02	0.13	3.88	0.08	2.87	0.06
Reproduction	40.00	Insectivore	26.30	0.66	19.46	0.49	18.16	0.45	13.44	0.34
	40.00	Granivore (grain and seeds)	4.07	0.10	3.01	0.08	1.94	0.05	1.44	0.04
	40.00	Frugivore (fruit)	8.14	0.20	6.02	0.15	3.88	0.10	2.87	0.07
Medium Sized Bird (0.1 kg)										
Acute	23.20	Insectivore	20.53	0.88	15.19	0.65	14.17	0.61	10.49	0.45
	23.20	Granivore (grain and seeds)	3.18	0.14	2.35	0.10	1.51	0.07	1.12	0.05
	23.20	Frugivore (fruit)	6.35	0.27	4.70	0.20	3.03	0.13	2.24	0.10
Dietary	47.00	Insectivore	20.53	0.44	15.19	0.32	14.17	0.30	10.49	0.22
	47.00	Granivore (grain and seeds)	3.18	0.07	2.35	0.05	1.51	0.03	1.12	0.02
		Frugivore (fruit)	6.35	0.14	4.70	0.10	3.03	0.06	2.24	0.05
Reproduction	40.00	Insectivore	20.53	0.51	15.19	0.38	14.17	0.35	10.49	0.26
	40.00	Granivore (grain and seeds)	3.18	0.08	2.35	0.06	1.51	0.04	1.12	0.03
		Frugivore (fruit)	6.35	0.16	4.70	0.12	3.03	0.08	2.24	0.06
Large Sized Bird (1 kg)										
Acute	23.20	Insectivore	5.99	0.26	4.43	0.19	4.14	0.18	3.06	0.13
	23.20	Granivore (grain and seeds)	0.93	0.04	0.69	0.03	4.14	0.18	0.33	0.01
	23.20	Frugivore (fruit)	1.85	0.08	1.37	0.06	0.88	0.04	0.65	0.03
	23.20	Herbivore (short grass)	13.26	0.57	9.81	0.42	4.71	0.20	3.48	0.15
	23.20	Herbivore (long grass)	8.10	0.35	5.99	0.26	2.64	0.11	1.96	0.08
	23.20	Herbivore (Broadleaf plants)	12.27	0.53	9.08	0.39	4.06	0.17	3.00	0.13
Dietary	47.00	Insectivore	5.99	0.13	4.43	0.09	4.14	0.09	3.06	0.07
	47.00	Granivore (grain and seeds)	0.93	0.02	0.69	0.01	4.14	0.09	0.33	0.01
	47.00	Frugivore (fruit)	1.85	0.04	1.37	0.03	0.88	0.02	0.65	0.01
	47.00	Herbivore (short grass)	13.26	0.28	9.81	0.21	4.71	0.10	3.48	0.07

	Toxicity (mg ai/kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field (74%)		On-field		Off Field (74%)	
			EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ
	47.00	Herbivore (long grass)	8.10	0.17	5.99	0.13	2.64	0.06	1.96	0.04
	47.00	Herbivore (Broadleaf plants)	12.27	0.26	9.08	0.19	4.06	0.09	3.00	0.06
Reproduction	40.00	Insectivore	5.99	0.15	4.43	0.11	4.14	0.10	3.06	0.08
	40.00	Granivore (grain and seeds)	0.93	0.02	0.69	0.02	4.14	0.10	0.33	0.01
	40.00	Frugivore (fruit)	1.85	0.05	1.37	0.03	0.88	0.02	0.65	0.02
	40.00	Herbivore (short grass)	13.26	0.33	9.81	0.25	4.71	0.12	3.48	0.09
	40.00	Herbivore (long grass)	8.10	0.20	5.99	0.15	2.64	0.07	1.96	0.05
	40.00	Herbivore (Broadleaf plants)	12.27	0.31	9.08	0.23	4.06	0.10	3.00	0.08
<b>Small Sized Mammal (0.015 kg)</b>										
Acute	30.00	Insectivore	15.13	0.50	11.19	0.37	10.45	0.35	7.73	0.26
	30.00	Granivore (grain and seeds)	2.34	0.08	1.73	0.06	1.12	0.04	0.83	0.03
	30.00	Frugivore (fruit)	4.68	0.16	3.46	0.12	2.23	0.07	1.65	0.06
Reproduction	7.8	Insectivore	15.13	<b>1.94</b>	11.19	<b>1.44</b>	10.45 10.45	<b>1.34</b>	7.73	0.99
	7.8	Granivore (grain and seeds)	2.34	0.30	1.73	0.22	1.12	0.14	0.83	0.11
	7.8	Frugivore (fruit)	4.68	0.60	3.46	0.44	2.23	0.29	1.65	0.21
<b>Medium Sized Mammal (0.035 kg)</b>										
Acute	30.00	Insectivore	13.26	0.44	9.81	0.33	9.16	0.31	6.78	0.23
	30.00	Granivore (grain and seeds)	2.05	0.07	1.52	0.05	0.98	0.03	0.72	0.02
	30.00	Frugivore (fruit)	4.10	0.14	3.04	0.10	1.96	0.07	1.45	0.05
	30.00	Herbivore (short grass)	29.34	0.98	21.71	0.72	10.42	0.35	7.71	0.26
	30.00	Herbivore (long grass)	17.91	0.60	13.26	0.44	5.85	0.20	4.33	0.14
	30.00	Herbivore (forage crops)	27.15	0.90	20.09	0.67	8.97	0.3	6.64	0.22
Reproduction	7.8	Insectivore	13.26	<b>1.70</b>	9.81	<b>1.26</b>	9.16	<b>1.17</b>	6.78	0.87
	7.8	Granivore (grain and seeds)	2.05	0.26	1.52	0.19	0.98	0.13	0.72	0.09
	7.8	Frugivore (fruit)	4.10	0.53	3.04	0.39	1.96	0.25	1.45	0.19
	7.8	Herbivore (short grass)	29.34	<b>3.76</b>	21.71	<b>2.78</b>	10.42	<b>1.34</b>	7.71	0.99
	7.8	Herbivore (long grass)	17.91	<b>2.30</b>	13.26	<b>1.70</b>	5.85	0.75	4.33	0.56
	7.8	Herbivore (Broadleaf plants)	27.15	<b>3.48</b>	20.09	<b>2.58</b>	8.97	<b>1.15</b>	6.64	0.85
<b>Large Sized Mammal (1 kg)</b>										
Acute	30.00	Insectivore	7.09	0.24	5.24	0.17	4.89	0.16	3.62	0.12
	30.00	Granivore (grain and seeds)	1.10	0.04	0.81	0.03	0.52	0.02	0.39	0.01
	30.00	Frugivore (fruit)	2.19	0.07	1.62	0.05	1.05	0.03	0.77	0.03
	30.00	Herbivore (short grass)	15.68	0.52	11.60	0.39	5.57	0.19	4.12	0.14
	30.00	Herbivore (long	9.57	0.32	7.08	0.24	3.13	0.10	2.31	0.08

	Toxicity (mg ai/kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field (74%)		On-field		Off Field (74%)	
			EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ	EDE (mg a.i./k g bw)	RQ
		grass)								
	30.00	Herbivore (Broadleaf plants)	14.50	0.48	10.73	0.36	4.79	0.16	3.55	0.12
Reproduction	7.8	Insectivore	7.09	0.91	5.24	0.67	4.89	0.63	3.62	0.46
	7.8	Granivore (grain and seeds)	1.10	0.14	0.81	0.10	0.52	0.07	0.39	0.05
	7.8	Frugivore (fruit)	2.19	0.28	1.62	0.21	1.05	0.14	0.77	0.10
	7.8	Herbivore (short grass)	15.68	<b>2.04</b>	11.60	<b>1.51</b>	5.57	0.72	4.12	0.50
	7.8	Herbivore (long grass)	9.57	<b>1.23</b>	7.08	0.92	3.13	0.40	2.31	0.30
	7.8	Herbivore (Broadleaf plants)	14.50	<b>1.86</b>	10.73	<b>1.39</b>	4.79	0.61	3.55	0.45

<sup>a</sup> EDE = Estimated daily exposure; is calculated using the following formula: (FIR/BW) × EEC. Where FIR is Food Ingestion Rates (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:

Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) =  $0.398(BW \text{ in g})^{0.850}$

All birds Equation (body weight > 200 g): FIR (g dry weight/day) =  $0.648(BW \text{ in g})^{0.651}$

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) =  $0.235(BW \text{ in g})^{0.822}$

At the screening level, food items representing the most conservative EEC for each size guild are used.

**Table 26 Risk assessment for birds and mammals consuming flupyradifurone treated soybean seeds**

	Study Endpoint (mg a.i./kg bw/day / UF)	EDE (mg a.i./kg bw/day)	RQ	Number of seeds needed to reach endpoint	Area required to reach the endpoint (m <sup>2</sup> )	
					100% seeds available	1% seeds available
Small bird (0.02 kg)						
Acute	23.20	86.34	3.72	6.82	0.1	-
Dietary	47.00	86.34	1.84	13.82	0.2	-
Reproduction	40.00	86.339	2.16	11.76	0.2	-
Medium bird (0.10 kg)						
Acute	23.20	67.821	2.92	34.12	0.6	61.4
Dietary	47.00	67.821	1.44	69.12	1.2	124.4
Reproduction	40.00	67.821	1.70	58.82	1.1	105.9
Large bird (1.00 kg)						
Acute	23.20	19.772	0.85	341.18	6.1	-
Dietary	47.00	19.772	0.42	691.18	12.4	-
Reproduction	40.00	19.772	0.49	588.24	10.6	-
Small mammals (0.015 kg)						
Acute	30.00	49.340	1.64	6.62	0.1	11.9
Reproduction	7.8	49.340	6.33	1.72	0.0	3.1
Medium mammals (0.035 kg)						
Acute	30.00	42.433	1.41	15.44	0.3	27.8
Reproduction	7.8	42.433	5.44	4.01	0.1	7.2
Large mammals (1.00 kg)						
Acute	30.00	23.364	0.78	441.18	7.9	794.1
Reproduction	7.8	23.364	3.00	114.71	2.1	206.5



**Table 27 Risk assessment of BYI 02960 SL 200 to non-target terrestrial vascular plants at a single application of 400 g a.i./ha.**

Exposure	Endpoint g a.i./ha	EEC g a.i./ha	RQ	Risk
Seedling emergence	>410	400	< 1	Negligible risk
Vegetative vigour	>410	400	< 1	Negligible risk

**Table 28 Screening level risk to aquatic organisms**

Organism	Test item	Exposure	Endpoint value (mg/L)	EEC (mg a.i./L) *		RQ	LOC exceeded?
				15 cm	80 cm		
Freshwater species							
<i>Daphnia magna</i>	Flupyra-difurone	Acute	> 77.6	-	0.05	0.006	No
		Chronic	3.42	-	0.05	0.015	No
	6-CNA	Acute	> 95.1	-	0.09	< 0.02	No
	DFA	Acute	> 10.2	-	0.15	< 0.03	No
	BYI 02960-succinamide	chronic	46.3	-	0.047	0.001	No
Chironomus	Flupyra-difurone	Acute	0.064	-	0.05	<b>1.56</b>	<b>Yes</b>
		Chronic	0.0105	-	0.05	<b>4.55</b>	<b>Yes</b>
	BYI 02960-succinamide	Acute	> 104.5	-	0.047	< 0.001	No
	BYI 02960-azabicyclo-succinamide	Acute	> 114.5	-	0.05	< 0.0009	No
	6-CNA	Acute	> 1	-	0.09	< 0.09	No
		Chronic	102	-	0.09	0.0009	No
DFA	Chronic	105	-	0.15	0.003	No	
Amphibian	Flupyra-difurone	Acute	> 73.8	0.27	-	0.04	No
Fresh water fish	Flupyra-difurone	Acute	> 70.5	-	0.05	0.007	No
		Chronic	4.41	-	0.05	0.011	No
	BYI 02960-succinamide	Acute	> 114	-	0.047	< 0.004	No
	DFA	Acute	> 10.35	-	0.15	< 0.15	No
Freshwater alga	Sivanto	Acute	> 42.8	-	0.05	< 0.002	No
	6-CNA		> 100	-	0.09	< 0.0009	No
	DFA		> 10.2	-	0.15	< 0.015	No
	BYI 02960-succinamide		> 11.4	-	0.047	< 0.004	No
Vascular plant	Flupyra-difurone	Acute	> 67.6	-	0.05	0.001	No
Mysid shrimp	Flupyra-difurone	Acute	> 0.25	-	0.05	0.4	No
		Chronic	0.013	-	0.05	<b>3.85</b>	<b>Yes</b>
Mollusk	Flupyra-difurone	Acute	> 29	-	0.05	0.003	No
Salt water fish	Flupyra-difurone	Acute	> 83.9	-	0.05	0.006	No



\* EECs calculated for transformation products were based on 100% conversion from the parent compound, the most conservative scenario.

**Table 29 Refined risk assessment of BYI 02960 SL 200 to non-target aquatic organisms via spray drift to an 80 cm deep water body**

Organism	Exposure	Endpoint mg a.i./L	Off-field					
			26% drift (aerial, fine droplets)		11% drift (ground spray, fine droplets)		74% drift (early airblast, fine droplets)	
			EEC mg a.i./L	RQ	EEC mg a.i./L	RQ	EEC mg a.i./L	RQ
Chironomus	Acute	0.068	0.013	0.41	0.0055	0.17	0.037	1.15
	Chronic	0.011	0.013	1.18	0.0055	0.5	0.037	3.36
Salt water mysid	Chronic	0.013	0.013	1.0	0.0055	0.42	0.037	2.85

**Table 30 Refined risk assessment of BYI 02960 SL 200 to non-target aquatic organisms via run-off and pore water in an 80 cm deep water body**

Organism	Exposure	Endpoint µg a.i./L	Peak concentration		21-Day concentration		LOC exceeded?
			EEC µg a.i./L	RQ	EEC mg a.i./L	RQ	
Run-off							
Chironomus	Chronic	11	40	3.64	39	3.55	Yes
Salt water mysid	Chronic	13	40	3.08	39	3.0	Yes
Pore water							
Chironomus	Chronic	11	25	2.27	25	2.27	Yes

**Table 31 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria**

Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria					
TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient	Major transformation products	
				DFA	6-CNA
CEPA toxic or CEPA toxic equivalent <sup>1</sup>	Yes		Yes	Yes	Yes
Predominantly anthropogenic <sup>2</sup>	Yes		Yes	Yes	Yes
Persistence <sup>3</sup> :	Soil	Half-life ≥ 182 days	Yes 188 (90 confidence bound on mean of ten half-life values adjusted to 25°C)	No 49 (90 % confidence bound on mean of three values adjusted to 25°C)	No (2.1 – 4.0 days)
	Whole system	Half-life ≥ 182 days	Yes (1740, max of two values)	Yes (672, max of two values)	NA
	Water	Half-life ≥ 182 days	NA	NA	NA
	Sediment	Half-life ≥ 365 days	NA	NA	NA

Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria					
TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient	Major transformation products	
				DFA	6-CNA
	Air	Half-life $\geq 2$ days or evidence of long range transport	No 4.4 – 13.1 hours	NA	NA
Bioaccumulation <sup>1</sup>	Log K <sub>ow</sub> $\geq 5$		No 1.2 (at pH 7)	No	No
	BCF $\geq 5000$		NA	NA	NA
	BAF $\geq 5000$		NA	NA	NA
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

<sup>1</sup>All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e. all other TSMP criteria are met).

<sup>2</sup>The policy considers a substance “predominantly anthropogenic” if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

<sup>3</sup> If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

<sup>4</sup>Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K<sub>ow</sub>).

**Table 32 Uses of SIVANTO 200 SL (maximum rate/crop/year is 400 g flupyradifurone/ha)**

Crops	Pests	Rate	Appl. Method	Min. Appl. Interval
Crop Subgroup 1C (Tuberous and Corn Vegetables)	aphids, leafhoppers	500-750 mL/ha	Foliar,	10 days
	whiteflies, Colorado potato beetle	750-1000 mL/ha	Ground, Aerial	
Crop Subgroup 1B (Root Vegetables, except sugarbeet)	aphids, leafhoppers	500-750 mL/ha	Foliar,	10 days
	whiteflies	750-1000 mL/ha	Ground, Aerial	
Crop Group 4-13 (Leafy Vegetables), Crop Group 5-13 (Brassica Head and Stem Vegetables), Crop Subgroup 22B (Leaf Petiole Vegetables)	aphids	500-750 mL/ha	Foliar,	7 days
	whiteflies	750-1000 mL/ha	Ground	
Crop Group 6 (Legume Vegetables)	aphids, leafhoppers	500-750 mL/ha	Foliar,	10 days
	whiteflies	750-1000 mL/ha	Ground, Aerial	
Crop Group 8-09 (Fruiting Vegetables)	aphids, leafhoppers	500-750 mL/ha	Foliar,	10 days
	whiteflies, Colorado potato beetle	750-1000 mL/ha	Ground	
	aphids, whiteflies	750-1000 mL/ 10,000 plants	Soil; Ground	N/A
Crop Group 9 (Cucurbit Vegetables)	aphids, leafhoppers	500-750 mL/ha	Foliar,	7 days
	whiteflies,	750-1000 mL/ha	Ground	
	aphids, leafhoppers, whiteflies	750-1000 mL/ 10,000 plants	Soil; Ground	N/A

Crops	Pests	Rate	Appl. Method	Min. Appl. Interval
Crop Group 11-09 (Pome Fruit)	aphids (except woolly apple aphid), leafhoppers	500-750 mL/ha	Foliar; Ground	10 days
	San Jose scale, oystershell scale, pear psylla (suppression)	750-1000 mL/ha + 0.25 % v/v horticultural oil		
Crop Subgroup 13-07B (Berry and Small Fruit, except highbush cranberry)	aphids	500-750 mL/ha	Foliar;	7 days
	blueberry maggot	750-1000 mL/ha	Ground	
Crop Subgroup 13-07F (Berry and Small Fruit - vine including grapes)	leafhoppers	500-750 mL/ha	Foliar; Ground	10 days
	leafhoppers	1500-2000 mL/ha	Soil; Ground	N/A
Crop Subgroup 13-07G (Berry and Small Fruit - low growing berries including strawberries, except lowbush blueberry and lowbush cranberry)	aphids	500-750 mL/ha	Foliar; Ground	10 days
	blueberry maggot	750-1000 mL/ha		
Crop Group 14-11 (Tree Nuts)	aphids	500-750 mL/ha	Foliar; Ground	14 days
Corn (field, sweet, pop, seed)	aphids	500-750 mL/ha	Foliar; Ground, Aerial	7 days
Alfalfa	aphids, leafhoppers	500-750 mL/ha	Foliar; Ground	10 days
Peanuts	aphids, leafhoppers	500-750 mL/ha	Foliar;	10 days
	whiteflies	750-1000 mL/ha	Ground	
Hops	aphids	500-750 mL/ha	Foliar; Ground	N/A

**Table 33 Uses of BYI 02960 480 FS (maximum rate/crop/year is 400 g flupyradifurone/ha)**

Crop	Pests	Appl. Method	Rate	Tank mix partners
soybean	soybean aphid, bean leaf beetle adults	Seed treatment	13.3-20.0 mL/140,000 seeds	EverGol Energy, EverGol Xtend, Allegiance FL, Trilex AL Concentrate, Trilex FS

## Appendix II Supplemental Maximum Residue Limit Information— International Situation and Trade Implications

Flupyradifurone is a new active ingredient which is concurrently being registered in Canada and the United States. The MRLs proposed for flupyradifurone in Canada are the same as corresponding tolerances to be promulgated in the United States, except for certain livestock commodities, in accordance with Table 1 below, for which differences in MRLs/tolerances may be due to different livestock feed items and practices.

Once established, the American tolerances for flupyradifurone will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs<sup>9</sup> listed for flupyradifurone in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

Table 1, below, compares the MRLs proposed for flupyradifurone in Canada with corresponding American tolerances. American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food website, by pesticide or commodity }.

**Table 1 Comparison of Canadian MRLs, and American Tolerances.**

Commodity	Canadian MRL (ppm)	American Tolerance (ppm)
Brassica leafy greens (CG4-13B)	40	40 (CG4B)
Leafy greens (CG4-13A)	30	30 (CG4A)
Hops (dried)	10	10
Leaf petiole vegetables (CG22B)	9.0	9.0 (leaf petioles; CG4B)
Brassica head and stem vegetable group (CG5-13)	6.0	6.0 (CG5A)
Raisins	5.0	5.0
Bushberry (CG13-07B, except highbush cranberries)	4.0	4.0
Green onions (CG3-07B)	3.0	3.0
Citrus fruits (revised) (CG10-R)	3.0	3.0 (CG10-10)
Edible-podded legume vegetables (CG6A)	3.0	
Small fruit vine climbing subgroup (CG13-07F, except fuzzy kiwifruit)	3.0	3.0
Cereal grains (CG15, except rice, field corn, popcorn grain, and sweet corn kernels plus cob with husks removed)	3.0	3.0
Dried shelled pea and bean (CG6C, except soybean)	3.0	3.0
Succulent shelled English peas	2.0	2.0 (Succulent shelled peas)
Succulent shelled garden peas	2.0	
Succulent shelled green peas	2.0	
Succulent shelled peas	2.0	
Succulent shelled pigeon peas	2.0	
Fruiting vegetables (CG8-09)	1.5	1.5 (CG8-10)

<sup>9</sup> The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.



Commodity	Canadian MRL (ppm)	American Tolerance (ppm)
Low growing berry (CG13-07G, except lowbush blueberries and cranberries)	1.5	1.5
Dry soybeans	1.5	1.5
Green coffee beans	1.5	1.5
Root vegetable (CG1B, except sugar beet)	0.9	0.9
Undelinted cotton seeds (CG20C-R)	0.8	0.8
Pome fruits (CG11-09)	0.7	0.7 (CG11-10)
Prickly pear pads	0.7	0.7
Meat byproducts of cattle, goats, horses, and sheep	0.5	1.0
Cucurbit vegetables (CG9)	0.4	0.4
Prickly pears	0.3	0.3
Succulent shelled blackeyed peas	0.2	0.2 (Succulent shelled beans)
Succulent shelled broad beans	0.2	
Succulent shelled cowpeas	0.2	
Succulent shelled lima beans	0.2	
Succulent shelled southern peas	0.2	
Meat of cattle, goats, horses, and sheep	0.15	0.3
Bulb onions (CG3-07A)	0.09	0.09
Fat of cattle, goats, horses, and sheep	0.06	0.2
Milk	0.06	0.15
Tuberous and corm vegetables (CG1C)	0.05	0.05
Field corn, and popcorn grain	0.05	0.05
Sweet corn kernels plus cob with husks removed	0.05	0.05
Peanuts	0.04	0.04
Meat byproducts of hogs	0.02	0.04
Tree nuts (CG14-11)	0.02	0.02
Fat, meat and meat byproducts of poultry	0.01	None
Eggs	0.01	0.01
Fat and meat of hogs	0.01	0.01

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the crop field trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

## References

### A. List of Studies/Information Submitted by Registrant

#### 1.0 Chemistry

PMRA Document Number	Reference
2239051	2012, Flupyradifurone (BYI 02960), technical substance : Relative density, DACO: 2.14.6.IIA 2.2
2239052	2012, Flupyradifurone (BYI 02960), pure substance: Relative density, DACO: 2.14.6.IIA 2.2
2239098	2012, BYI 02960, pure substance: Solubility in distilled water (pH 7), at pH 4 and pH 9 (flask method), DACO: 2.14.7.IIA 2.6
2239104	2011, Flupyradifurone (BYI 02960): Solubility in organic solvents, DACO: 2.14.8.IIA 2.7
2239184	2012, Flupyradifurone (BYI 02960), technical substance: explosive properties, DACO: 2.16.IIA 2.13
2239221	2012, Flupyradifurone (BYI 02960), technical substance : Determination of the surface tension, DACO: 2.16.IIA 2.14
2239222	2011, Flupyradifurone (BYI 02960), technical substance: oxidizing properties, DACO: 2.16.IIA 2.15
2239224	2012, Flupyradifurone (BYI 02960), technical substance : Determination of the pH-value in distilled water, DACO: 2.16.IIA 2.16
2239226	2012, Flupyradifurone (BYI 02960), pure substance: Determination of the pH-value in distilled water, DACO: 2.16.IIA 2.16
2239228	2012, Flupyradifurone (BYI 02960), technical substance: Statement on the viscosity according to OPPTS 830.7100, DACO: 2.16.IIA 2.18
2239229	2012, Flupyradifurone (BYI 02960), technical substance: Statement on the miscibility according to OPPTS 830.6319, DACO: 2.16.IIA 2.18
2239230	2012, Flupyradifurone (BYI 02960), technical substance: Complex formation ability in water, DACO: 2.16.IIA 2.18
2239232	2012, Flupyradifurone (BYI 02960), technical substance: Particle size distribution, DACO: 2.16.IIA 2.18
2239233	2012, Flupyradifurone (BYI 02960), technical substance : The oxidation or reduction properties, DACO: 2.16.IIA 2.18
2239234	2011, Flupyradifurone (BYI 02960), technical substance: Statement on the dielectric breakdown voltage according to OPPTS 830.6321, DACO: 2.16.IIA 2.18
2239236	2011, BYI 02960 - Determination of [CBI REMOVED], DACO: 2.16.IIA 2.18 CBI
2239249	2012, Flupyradifurone (BYI 02960), technical substance: Melting point, boiling point, thermal stability, DACO: 2.14.13.2.14.4.2.14.5.IIA 2.1.1.IIA 2.1.2.IIA 2.1.3
2239250	2012, BYI 02960, pure substance: Melting point, boiling point, thermal stability, DACO: 2.14.13.2.14.4.2.14.5.IIA 2.1.1.IIA 2.1.2.IIA 2.1.3
2239251	2012, Flupyradifurone (BYI 02960), technical substance: flammability (solids), DACO: 2.16.IIA 2.11.1
2239252	2012, Flupyradifurone (BYI 02960), pure substance: Partition coefficient 1-octanol / water at pH 4, pH 7 and pH 9 (HPLC-method), DACO: 2.14.11.IIA 2.8.1.IIA 2.8.2

PMRA Document Number	Reference
2239253	2012, Material accountability of technical flupyradifurone (BYI 02960) - Five batches of technical flupyradifurone, DACO: 2.13.3,IIA 1.11.1 CBI
2239295	2012, Chemical storage stability of BYI 02960 - Flupyradifurone (BYI 02960), DACO: 2.14.14,IIA 2.17.1
2239296	2012, Flupyradifurone (BYI 02960), technical substance: Physical characteristics colour, physical state and odour, DACO: 2.14.1,2.14.2,2.14.3,IIA 2.4.1,IIA 2.4.2
2239297	2012, Flupyradifurone (BYI 02960), pure substance - Physical characteristics colour, physical state and odour, DACO: 2.14.1,2.14.2,2.14.3,IIA 2.4.1,IIA 2.4.2
2239298	2008, BYI 02960, pure substance: Vapour pressure - Final report, DACO: 2.14.9,8.2.4.5,IIA 2.3.1,IIA 7.4.9
2239299	2012, Flupyradifurone (BYI 02960) - Determination of technical grade active substance HPLC - ISTD, DACO: 2.13.1,IIA 4.2.1
2239300	2011, Validation of AM008809MP1 - Flupyradifurone (BYI 02960) - Determination of technical grade active substance HPLC - ISTD, DACO: 2.13.1,IIA 4.2.1
2239381	2012, Flupyradifurone (BYI 02960) - Description of the manufacturing process of the technical grade active substance, DACO: 2.11.1,2.11.2,2.11.3,2.11.4,IIA 1.8.1,IIA 1.8.2 CBI
2239382	2012, Flupyradifurone (BYI 02960), technical substance: autoflammability (UN Bowes Cameron cage test), DACO: 2.16,IIA 2.11.2
2239383	2012, Flupyradifurone (BYI 02960), technical substance: auto-flammability, DACO: 2.16,IIA 2.11.2
2239384	2012, Material accountability of technical flupyradifurone (BYI 02960) - One batch of technical flupyradifurone, DACO: 2.13.3,IIA 1.11.2 CBI
2239399	2012, Material accountability of technical flupyradifurone (BYI 02960) - One batch of technical flupyradifurone, DACO: 2.13.3,IIA 1.11.2 CBI
2239400	2012, BYI 02960 - Toxicological equivalence assessment of the technical specification with the material tested in toxicity studies, DACO: 2.13.3,IIA 1.11.2
2239401	2012, Flupyradifurone (BYI 02960) - Technical grade active substance - Discussion of the formation of impurities, DACO: 2.12.2,2.13.4,IIA 1.10.2 CBI
2239412	2012, Stability to normal and elevated temperature, metals, and metal ions and corrosion characteristics to plastic containers of flupyradifurone (BYI 02960) according to OPPTS 830.6313 and 830.6320, DACO: 2.14.13,IIA 2.17.2
2239413	2012, Flupyradifurone (BYI 02960): Calculation of the Henrys law constant, DACO: 2.16,8.2.4.5,IIA 2.3.2,IIA 7.4.9
2239482	2011, Composition statement technical grade active substance - Flupyradifurone, DACO: 2.12.2,IIA 1.9.3 CBI
2239484	2012, Confidential statement of formula (basic) - flupyradifurone TC, DACO: 2.12.2,IIA 1.9.3 CBI
2239485	2012, Statement of product specification form - Flupyradifurone TC, DACO: 2.12.2,IIA 1.9.3 CBI
2239491	2012, Analytical method - Flupyradifurone (BYI 02960) polar impurities in technical grade active substance HPLC - external standard, DACO: 2.13.1,2.13.4,IIA 4.2.3 CBI
2239492	2012, Validation of AM014011MP2 - Flupyradifurone (BYI 02960) polar impurities in technical grade active substance HPLC-ESTD, DACO: 2.13.1,2.13.4,IIA 4.2.3 CBI
2239493	2012, Validation of AM013011MP2 - Flupyradifurone (BYI 02960) - Impurities in technical grade active substance - HPLC-ESTD, DACO: 2.13.1,2.13.4,IIA 4.2.3 CBI



PMRA Document Number	Reference
2239495	2012, Validation of AM016411MPI - Determination of [CBI REMOVED]in flupyradifurone (BYI 02960), DACO: 2.13.1,2.13.4,IIA 4.2.3 CBI
2239496	2012, Flupyradifurone (BYI 02960) - Determination of [CBI REMOVED]in flupyradifurone (BYI 02960), DACO: 2.13.1,2.13.4,IIA 4.2.3
2239497	2012, Validation of GLC-method AM015011MPI - Determination of [CBI REMOVED] in flupyradifurone - GLC - external standard ( Headspace ), DACO: 2.13.1,2.13.4,IIA 4.2.3 CBI
2239498	2012, Flupyradifurone - Determination of [CBI REMOVED] in flupyradifurone ( BYI 02960 ) GLC - external standard ( Headspace ), DACO: 2.13.1,2.13.4,IIA 4.2.3 CBI
2239499	2012, Flupyradifurone (BYI 02960) - Impurities in technical grade active substance - HPLC - external standard, DACO: 2.13.1,2.13.4,IIA 4.2.3 CBI
2239542	2012, Flupyradifurone (BYI 02960), pure substance : Dissociation constant in water, DACO: 2.14.10,8.2.3.2,IIA 2.9.5
2239594	2012, Spectral data set of BYI 02960 a.i. - Reference material, DACO: 2.13.2,2.14.12,IIA 2.5.1.1,IIA 2.5.1.2,IIA 2.5.1.3,IIA 2.5.1.4,IIA 2.5.1.5
2284002	2013, Bayer CropScience (BCS) Response To Completeness Check Clarifications/Deficiencies Related To Global Joint Review Submissions Of Flupyradifurone Technical, Sivanto 200 SL & BYI 02960 480 FS, DACO: 2.11.2,2.11.4,2.13.2,2.13.4,4.2.6,4.3.6,4.5.12,4.5.13 CBI
2287602	2013, Spectral data (NMR and MS) for impurities in FLUPYRADIFURONE (BYI 02960) technical material, DACO: 2.13.2 CBI
2432153	2014, Flupyradifurone (BYI 02960), Technical substance: Physical characteristics colour and physical state, DACO: 2.14.1,2.14.2 CBI
2239081	2010, An analytical method for the determination of residues of BYI 02960, 6-chloronicotinic acid (6-CNA) and difluoroacetic acid (DFA) in soil and sediment using LC/MS/MS, DACO: 8.2.2.1,IIA 4.4
2239082	2009, Analytical method 01074 for the determination of BYI 02960 in soil using LC/MS/MS, DACO: 8.2.2.1,IIA 4.4
2239084	2012, In house laboratory validation of an analytical method for the determination of residues of BYI 02960 and its metabolites 6-chloronicotinic acid (6-CNA) and difluoroacetic acid (DFA) in soil and sediment using LC/MS/MS, DACO: 8.2.2.1,IIA 4.4
2239085	2011, Bayer method RV-002-S10-02 - An analytical method for the determination of residues of BYI 02960, 6-chloronicotinic acid (6-CNA) and difluoroacetic acid (DFA) in soil and sediment using LC/MS/MS, DACO: 8.2.2.1,IIA 4.4
2239087	2012, Independent laboratory validation of Bayer method RV-002-S10-02 for the determination of BYI 02960 and its two acid metabolites in soil and sediment, DACO: 8.2.2.1,IIA 4.4
2239091	2012, Analytical method no 01213 for the determination of residues of BYI 02960 in drinking and surface water by HPLC-MS/MS, DACO: 8.2.2.3,IIA 4.5
2239092	2012, In house laboratory validation of an analytical method for the determination of residues of BYI 02960 and its metabolites difluoroacetic acid, BYI 02960-succinamide and BYI 02960-azabicyclosuccinamide in water using LC/MS/MS, DACO: 8.2.2.3,IIA 4.5



PMRA Document Number	Reference
2239093	2012, Independent laboratory validation of Bayer method - RV-005-W12-01 Analytical method for the determination of residues of BYI 02960 and its metabolites difluoroacetic acid, BYI 02960-succinamide, BYI 02960-azabicyclosuccinamide in water using LC/MS/MS, DACO: 8.2.2.3,IIA 4.5
2239094	2012, Bayer method RV-005-W12-01 - Analytical method for the determination of residues of BYI 02960 and its metabolites Difluoroacetic acid, BYI 2960-Succinamide and BYI 2960-Azabicyclosuccinamide in water using LC/MS/MS, DACO: 8.2.2.3,IIA 4.5
2236526	2012, Determination of BYI 02960 in formulations - Assay HPLC, external standard, DACO: 3.4.1,IIIA 5.2.1
2236527	2010, Validation of HPLC-method AM012609MF1 - Determination of BYI 02960 in formulations - BYI 02960 FS 480 (480 g/L), DACO: 3.4.1,IIIA 5.2.1
2236529	2010, Storage stability and shelf life of BYI 02960 FS 480 (480 g/L) - [Packaging material: HDPE] - Interim report (18 weeks), DACO: 3.5.10,IIIA 2.7.1,IIIA 2.7.3,IIIA 2.7.4,IIIA 2.7.5
2236532	2010, Determination of safety-relevant data of BYI 02960 FS 480 (480 g/L), DACO: 3.5.11,3.5.12,3.5.8,IIIA 2.2.1,IIIA 2.2.2,IIIA 2.3.1,IIIA 2.3.3
2236533	2011, Storage stability data of BYI 02960 FS 480 (480 g/L) - Packaging material: HDPE -, DACO: 3.5.10,3.5.14,3.5.5,IIIA 2.13,IIIA 2.14,IIIA 2.7.2
2236535	2010, Physical, chemical and technical properties of BYI 02960 FS 480 (480 g/L), DACO: 3.5.1,3.5.2,3.5.3,3.5.6,3.5.7,3.5.9,3.7.8,2.2.1,8.2.2.2,8.2.3.6,IIIA 2.1,IIIA 2.10.1,IIIA 2.10.2,IIIA 2.4.2,IIIA 2.5.1,IIIA 2.5.2,IIIA 2.5.3,IIIA 2.6.1,IIIA 2.8.2,IIIA 2.8.3.1,IIIA 2.8.5.2,IIIA 2.8.6.1,IIIA 2.8.8.2
2236545	2012, Manufacturing procedure - Plant protection product - Flupyradifurone FS 480 (480 g/L) - BYI 2960 FS 480, DACO: 3.2.2,IIIA 1.4.5.1 CBI
2284013	2012, Storage stability and shelf life of flupyradifurone FS 480 (480 g/L) - [Packaging material: HDPE] - Final report (2 years), DACO: 3.5.10
2236628	2011, Physical, chemical and technical properties of BYI 02960 SL 200 (200 g/L) - BYI 02960 SL 200 G - Amendment no.: 1, DACO: 3.5.1,3.5.2,3.5.3,3.5.6,3.5.7,3.5.9,3.7.8,2.3.6,IIIA 2.1,IIIA 2.4.2,IIIA 2.5.1,IIIA 2.5.2,IIIA 2.5.3,IIIA 2.6.1,IIIA 2.8.2,IIIA 2.8.4
2236631	2012, Storage stability data of BYI 02960 SL 200 (200 g/L) - [Packaging material:HDPE], DACO: 3.5.10,3.5.14,3.5.5,IIIA 2.13,IIIA 2.14,IIIA 2.7.2
2236632	2012, Storage stability and shelf life of BYI 02960 SL 200 (200 g/L) - [Packaging material:HDPE] - Final report (2 years), DACO: 3.5.10,3.5.14,IIIA 2.13,IIIA 2.7.2
2236635	2012, Safety relevant technical properties of BYI 02960 SL 200 (200 g/L) - Final report -, DACO: 3.5.11,3.5.12,3.5.8,IIIA 2.2.1,IIIA 2.2.2,IIIA 2.3.1,IIIA 2.3.3
2236642	2012, Determination of BYI 02960 in formulations - Assay HPLC, external standard, DACO: 3.4.1,IIIA 5.2.1
2236643	2010, Validation of HPLC-method AM012609MF1 - Determination of BYI 02960 in formulations - BYI 02960 SL 200 (200 g/L), DACO: 3.4.1,IIIA 5.2.1
2236690	2012, Manufacturing procedure plant protection product flupyradifurone SL 200 (200 g/L) - BYI 2960SL 200, DACO: 3.2.2,IIIA 1.4.5.1 CBI
2432163	2014, Appearance of flupyradifurone SL 200 (200 g/L), DACO: 3.5.1,3.5.2,3.5.3,3.5.6 CBI

## 2.0 Human and Animal Health

PMRA Document Number	Reference
2236513	2012, Local lymph node assay (LLNA) in mice - BYI 02960 480 FS, DACO: 4.6.6,IIIA 7.1.6
2236514	2012, Primary eye irritation study in rabbits - BYI 02960 480 FS, DACO: 4.6.4,IIIA 7.1.5
2236516	2012, Primary skin irritation study in rabbits - BYI 02960 480 FS, DACO: 4.6.5,IIIA 7.1.4
2236517	2012, Acute inhalation toxicity study in rats - BYI 02960 480 FS, DACO: 4.6.3,IIIA 7.1.3
2236520	2012, Acute dermal toxicity study in rats - BYI 02960 480 FS, DACO: 4.6.2,IIIA 7.1.2
2236522	2012, Acute oral toxicity up and down procedure in rats - BYI 02960 480 FS, DACO: 4.6.1,IIIA 7.1.1
2236640	2012, BYI 02960 SL 200 g/L - Acute toxicity in the rat after oral administration, DACO: 4.6.1,IIIA 7.1.1
2236649	2010, BYI 02960 SL 200 g/L - Acute toxicity in the rat after dermal application, DACO: 4.6.2,IIIA 7.1.2
2236651	2012, BYI 02960 SL 200 g/L - Acute inhalation toxicity in rats, DACO: 4.6.3,IIIA 7.1.3
2236668	2012, BYI 02960 SL 200 g/L - Acute skin irritation/corrosion on rabbits, DACO: 4.6.5,IIIA 7.1.4
2236678	2012, BYI 02960 SL 200 g/L - Acute eye irritation on rabbits, DACO: 4.6.4,IIIA 7.1.5
2236679	2012, BYI 02960 SL 200 g/L - Evaluation of potential skin sensitization in the local lymph node assay in the mouse, DACO: 4.6.6,IIIA 7.1.6
2239258	2012, [Pyridinylmethyl-14C]BYI 02960 - Absorption, distribution, excretion, and metabolism in the rat, DACO: 4.5.9,IIA 5.1.1
2239417	2011, [Furanone-4-14C]BYI 02960 - Absorption, distribution, excretion, and metabolism in the rat, DACO: 4.5.9,IIA 5.1.2
2239502	2011, [Ethyl-1-14C]BYI 02960 - Absorption, distribution, excretion, and metabolism in male rats, DACO: 4.5.9,IIA 5.1.3
2239418	2012, [Furanone-4-14C]BYI 02960 - Metabolism in organs and tissues of male and female rats, DACO: 4.5.9,IIA 5.1.2
2239503	2012, [Ethyl-1-14C]BYI 02960 - Metabolism in organs and tissues of male and female rats (3 time-points), DACO: 4.5.9,IIA 5.1.3
2239257	2011, Quantitative whole body autoradiography of [pyridinylmethyl-14C]BYI 02960 in male and female rats: Distribution of total radioactivity and elimination from blood, organs and tissues after single oral administration including determination of radioactivity in the excreta and exhaled 14CO <sub>2</sub> , DACO: 4.5.9,IIA 5.1.1
2239416	2011, Quantitative whole body autoradiography of [furanone-4-14C]BYI 02960 in male and female rats: Distribution of total radioactivity and elimination from blood, organs and tissues after single oral administration including determination of radioactivity in the excreta and exhaled 14CO <sub>2</sub> , DACO: 4.5.9,IIA 5.1.2
2239256	2012, BYI 02960 - Acute toxicity in the rat after oral administration, DACO: 4.2.1,IIA 5.2.1
2239415	2012, BYI 02960 - Acute toxicity in the rat after dermal administration, DACO: 4.2.2,IIA 5.2.2
2239500	2012, BYI 02960 - Activity ID TXRVP033 - Acute inhalation toxicity in rats, DACO: 4.2.3,IIA 5.2.3

PMRA Document Number	Reference
2239523	2009, BYI 02960 - Acute skin irritation/corrosion on rabbits, DACO: 4.2.5, IIA 5.2.4
2239543	2012, BYI 02960 - Acute eye irritation on rabbits, DACO: 4.2.4, IIA 5.2.5
2239544	2012, BYI 02960 - Local lymph node assay in mice (LLNA/IMDS), DACO: 4.2.6, IIA 5.2.6
2239546	2012, A subacute dermal toxicity study in rats with BYI 02960, DACO: 4.3.5, IIA 5.3.7
2284001	2013, Justification for Waiving a 90-Day Inhalation Study for BYI 02960, DACO: 4.3.6
2239302	2012, BYI 02960 : Preliminary 28-day toxicity study in the mouse by dietary administration, DACO: 4.3.3, IIA 5.3.1
2239436	2012, BYI 02960 - 90-day toxicity study in the mouse by dietary administration - Amendment no.2, DACO: 4.3.1, IIA 5.3.2
2239332	2012, BYI 02960 - Exploratory 28-day toxicity study in the rat by gavage, DACO: 4.3.3, IIA 5.3.1
2239311	2012, BYI 02960 - Exploratory 28-day toxicity study in the rat by dietary administration, DACO: 4.3.3, IIA 5.3.1
2239420	2012, BYI 02960 - 90-day toxicity study in the rat by dietary administration - Amendment no.2, DACO: 4.3.1, IIA 5.3.2
2239321	2012, Preliminary 28-day toxicity study in the dog by dietary administration, DACO: 4.3.3, IIA 5.3.1
2239504	2010, A 90-day toxicity feeding study in the beagle dog with technical grade BYi 02960, DACO: 4.3.2, IIA 5.3.3
2239521	2012, A chronic toxicity feeding study in the Beagle dog with technical grade BYI 02960, DACO: 4.3.2, IIA 5.3.4
2239506	2012, BYI 02960 - Carcinogenicity study in the C57BL/6J mouse by dietary administration, DACO: 4.4.3, IIA 5.5.3
2239460	2012, BYI 02960 - Chronic toxicity and carcinogenicity study in the Wistar rat by dietary administration, DACO: 4.4.2, 4.4.4, IIA 5.5.2
2239237	2012, Technical grade BYF 02960: A two-generation reproductive toxicity study in the Wistar rat, DACO: 4.5.1, IIA 5.6.1
2239547	2010, BYI 02960: Developmental toxicity study in the rat by gavage, DACO: 4.5.2, IIA 5.6.10
2351717	2013, BYI 02960 Range finding Study for Developmental Toxicity in the Rabbit by Gavage, DACO: 4.5.2
2239577	2012, BYI 02960 - Developmental toxicity study in the rabbit by gavage, DACO: 4.5.3, IIA 5.6.11
2239240	2011, BYI 02960 An acute neurotoxicity study in the rat by oral administration, DACO: 4.5.12, IIA 5.7.1
2239524	2011, BYI 02960 - A 90-day neurotoxicity study in the rat by dietary administration, DACO: 4.5.13, IIA 5.7.4
2239537	2012, A developmental neurotoxicity study with technical grade BYI 02960 in Wistar rats, DACO: 4.5.14, IIA 5.7.5
2239155	2012, BYI 02960: 28-day immunotoxicity study in the female wistar rat by dietary administration, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8, IIA 5.10
2239254	2012, BYI 02960 (tested as BYI 02960 technical) (project: BYI 02960) - Salmonella/microsome test plate incorporation and preincubation method, DACO: 4.5.4, IIA 5.4.1
2239255	2012, 1st amendment to report <i>Salmonella typhimurium</i> reverse mutation assay with BYI 02960, DACO: 4.5.4, IIA 5.4.1



PMRA Document Number	Reference
2239505	2012, BYI 02960 (tested as BYI 02960 technical) (project: BYI 02960) - V79/HPRT test in vitro for the detection of induced forward mutations, DACO: 4.5.5,IIA 5.4.3
2239414	2012, BYI 02960 (tested as BYI 02960 technical) - In vitro chromosome aberration test with chinese hamster V79 cells, DACO: 4.5.6,IIA 5.4.2
2239535	2012, BYI 02960 - Micronucleus-test on the male mouse, DACO: 4.5.7,IIA 5.4.4
2239536	2012, Micronucleus assay in bone marrow cells of the mouse with BYI 02960-a.i., DACO: 4.5.7,IIA 5.4.4
2239146	2012, Acute oral toxicity study in rats IM-0, DACO: 4.8,IIA 5.8
2239147	2012, Thirteen-week dietary subchronic toxicity study in rats IM-0, DACO: 4.8,IIA 5.8
2239148	2012, Reverse mutation study on bacteria IM-0, DACO: 4.8,IIA 5.8
2239149	1997, Acute oral toxicity study in rats IC-0, DACO: 4.8,IIA 5.8
2239150	2012, Reverse mutation study on bacteria IC-0, DACO: 4.8,IIA 5.8
2239132	2012, BCS-AA56716 - Acute oral toxicity in rats - Acute toxic class method, DACO: 4.8,IIA 5.8
2239105	2012, BCS-AA56716 (Difluoroacetic acid) - 90-day toxicity study in the rat by dietary administration, DACO: 4.8,IIA 5.8
2239122	2012, <i>Salmonella typhimurium</i> - Reverse mutation assay with BCS-AA56716 (metabolite of BYI 02960), DACO: 4.8,IIA 5.8
2239126	2012, BCS-AA56716 (metabolite of BYI 02960) - Gene mutation assay in Chinese hamster v79 cells in vitro (V79 / HPRT), DACO: 4.8,IIA 5.8
2239123	2012, BCS-AA56716 (metabolite of BYI 02960) - In vitro chromosome aberration test in Chinese hamster V79 cells, DACO: 4.8,IIA 5.8
2239133	2012, BYI-02960-difluoroethyl-amino-furanone acute oral toxicity in rats acute toxic class method, DACO: 4.8,IIA 5.8
2239154	2012, BYI 02960-difluoroethyl aminofuranone: A 28-day dietary toxicity study in wistar rats, DACO: 4.8,IIA 5.8
2239128	2012, <i>Salmonella typhimurium</i> reverse mutation assay with BYI 02960-difluoroethyl-amino-furanone (metabolite of byi-02960), DACO: 4.8,IIA 5.8
2239130	2012, BYI 0960-difluoroethyl-amino-furanone (metabolite of BYI 02960) - Gene mutation assay in Chinese hamster V79 cells in vitro (V79 / HPRT), DACO: 4.8,IIA 5.8
2239131	2012, BYI 02960-difluoroethyl-amino-furanone (metabolite of BYI 02960) - In vitro chromosome aberration test in Chinese hamster V79 cells, DACO: 4.8,IIA 5.8
2239152	2011, Micronucleus assay in bone marrow cells of the mouse with BYI 02960-difluoroethyl-amino-furanone (metabolite of BYI 02960), DACO: 4.8,IIA 5.8
2239153	2011, In vivo unscheduled DNA synthesis in rat hepatocytes with BYI 02960-difluoroethyl-amino-furanone (metabolite of BYI 02960), DACO: 4.8,IIA 5.8
2239156	2012, BYI 02960 - Biokinetic in the plasma of rats following 7 days exposure through the diet, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
1885209	2010, Observational study to determine dermal and inhalation exposure to workers in commercial seed treatment facilities: Mixing/treating with a liquid pesticide product and equipment clean-out, DACO: 5.6(A)
1965962	2008, Determination of operator exposure to imidacloprid during loading/sowing of Gaucho treated maize seeds under realistic field conditions in Germany and Italy, DACO: 5.6(A)
2236510	2012, Occupational exposure and risk assessment for BYI 02960 based seed treatment for use on soybeans in Canada and the United States, DACO: 5.10,5.3,5.6,5.7,5.9,IIIA 7.3.2,IIIA 7.4.1,IIIA 7.5.2



PMRA Document Number	Reference
2236512	2012, Laboratory dust-off study of soybean seeds treated with Sivanto 480FS seed treatment formulations, DACO: 4.6.8,4.7.7,4.8.5,14,IIIA 7.11
2004944	2010, Agricultural Handler Exposure Scenario Monograph: Open Cab Airblast Application of Liquid Sprays. Report Number AHE1006, DACO 5.3, 5.4
2115788	2008, Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients. Submission #2006-0257.
2236641	2012, BYI 02960 (SL200) - In vivo dermal absorption study in the male rat, DACO: 5.8,IIIA 7.6.1
2236650	2012, BYI 02960 (SL200) - Comparative in vitro dermal absorption study using human and rat skin, DACO: 5.8,IIIA 7.6.2
2239053	2011, Extraction efficiency testing of the residue analytical method RV-001-P10-02 for the determination of BYI 02960, 6-chloronicotinic acid, difluoroacetic acid and difluoroethyl-amino-furanone in plant matrices using aged radioactive residues, DACO: 7.2.1,7.2.4, IIA 4.3
2239060	2012, An analytical method for the determination of residues of BYI 02960 and its metabolites BYI 02960-hydroxy, BYI 02960-acetyl-AMCP, and difluoroacetic acid in animal matrices and biota using LC/MS/MS, DACO: 7.2.1,7.2.4, IIA 4.3
2239063	2012, BYI 02960 - Magnitude of the residue in dairy cows - Amended report, DACO: 7.2.1,7.2.4,7.3,7.5,7.6, IIA 4.3, IIA 6.1.1, IIA 6.4.2
2239069	2012, Independent laboratory validation - Bayer method RV-001-P10-02 for BYI 02960, 6-chloronicotinic acid, difluoroacetic acid, and difluoroethyl-amino-furanone in plant matrices using LC/MS/MS, DACO: 7.2.1,7.2.4, IIA 4.3
2239071	2010, Bayer Method RV-001-P10-02 - An analytical method for the determination of residues of BYI 02960, 6-chloronicotinic acid, difluoroacetic acid, and difluoroethyl-amino-furanone in plant matrices using LC/MS/MS, DACO: 7.2.1,7.2.4, IIA 4.3
2239072	2012, Independent laboratory validation of the residue analytical method: an analytical method for the determination of residues of BYI 02960 and its metabolites BYI 02960-hydroxy, BYI 02960-acetyl-AMCP, and difluoroacetic acid in animal matrices and biota using LC-MS/MS, Bayer Method No. RV-004-A11-04, DACO: 7.2.1,7.2.4, IIA 4.3
2239073	2012, BYI 02960 - Magnitude of the residue in laying hens, DACO: 7.2.1,7.2.4,7.5,7.6, IIA 4.3, IIA 6.4.1
2239074	2012, An analytical method for the determination of residues of BYI 02960, 6-chloronicotinic acid, difluoroacetic acid, and difluoroethyl-amino-furanone in plant matrices using LC/MS/MS, DACO: 7.2.1,7.2.4, IIA 4.3
2239075	2012, Amendment No. 1 - Validation of Bayer CropScience method RV-001-P10-02 - An analytical method for the determination of residues of BYI 02960, 6-chloronicotinic acid, difluoroacetic acid, and difluoroethyl-amino-furanone in plant matrices using LC/MS/MS, DACO: 7.2.1,7.2.4, IIA 4.3
2239239	2012, Storage stability of BYI 02960, difluoroacetic acid, and difluoroethyl-amino-furanone in plant matrices, DACO: 7.3, IIA 6.1.1
2239371	2011, Metabolism of [pyridinylmethyl-14C]BYI 02960 in potatoes, DACO: 6.3, IIA 6.2.1
2239372	2011, Metabolism of [furanone-4-14C]BYI 02960 in potatoes, DACO: 6.3, IIA 6.2.1
2239375	2011, Metabolism of [pyridinylmethyl-14C]BYI 02960 in apples, DACO: 6.3, IIA 6.2.1
2239376	2011, Metabolism of [pyridinylmethyl-14C]BYI 02960 in paddy rice, DACO: 6.3, IIA 6.2.1

PMRA Document Number	Reference
2239377	2011, Metabolism of [furanone-4-14C]BYI 02960 in paddy rice, DACO: 6.3, IIA 6.2.1
2239378	2011, Metabolism of [ethyl-1-14C]BYI 02960 in tomatoes, DACO: 6.3, IIA 6.2.1
2239379	2011, Metabolism of [pyridinylmethyl-14C]BYI 02960 in tomatoes, DACO: 6.3, IIA 6.2.1
2239380	2011, Metabolism of [furanone-4-14C]BYI 02960 in tomatoes, DACO: 6.3, IIA 6.2.1
2239392	2012, Determination of residues of difluoroacetic acid in extracts of samples from plant metabolism and confined rotational crops studies after application of BYI 02960, DACO: 6.3, IIA 6.2.1
2239393	2011, Metabolism of [furanone-4-14C]BYI 02960 in apples, DACO: 6.3, IIA 6.2.1
2239397	2011, Metabolism of [pyridinylmethyl-14C]BYI 02960 in cotton after spray application, DACO: 6.3, IIA 6.2.1
2239398	2011, Metabolism of [furanone-4-14C]BYI 02960 in cotton after spray application, DACO: 6.3, IIA 6.2.1
2239455	2012, [Furanone-4-14C]BYI 02960: Metabolism in the laying hen, DACO: 6.2, IIA 6.2.2
2239457	2012, [Pyridinylmethyl-14C]BYI 02960: Metabolism in the laying hen, DACO: 6.2, IIA 6.2.2
2239458	2012, Metabolism of [pyridinylmethyl-14C]BYI 02960 in confined rotational crops, DACO: 7.4.4, IIA 6.6.2
2239459	2011, Metabolism of [furanone-4-14C]BYI 02960 in confined rotational crops, DACO: 7.4.4, IIA 6.6.2
2239480	2011, [Furanone-4-14C]BYI 02960: Metabolism in the lactating goat, DACO: 6.2, IIA 6.2.3
2239481	2011, [Pyridinylmethyl-14C]BYI 02960: Metabolism in the lactating goat, DACO: 6.2, IIA 6.2.3
2239628	2012, BYI 02960 200 SL - Magnitude of the residue on root vegetables except sugar beets (CG 1B), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239631	2012, BYI 02960 200 SL - Magnitude of the residue in potato - Tuberous and corm vegetables (Crop Subgroup 1C), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239633	2012, BYI 02960 200 SL - Magnitude of the residue in/on bulb vegetables (crop group 3), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239637	2012, BYI 02960 SL 200 - Magnitude of the residue in/on leafy vegetables (Crop Group 4), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239638	2012, BYI 02960 200 SL - Magnitude of the residue in head and stem brassica (crop subgroup 5A), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239639	2012, BYI 02960 200 SL - Magnitude of the residue in leafy Brassica greens (Crop Subgroup 5B), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239640	2012, BYI 02960 200 SL - Magnitude of the residue in edible podded legume vegetables (crop subgroups 6A), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239641	2012, BYI 02960 200 SL - Magnitude of the residue in/on succulent, shelled pea and bean (crop subgroup 6B), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239643	2012, BYI 02960 200 SL - Magnitude of the residue in/on dried, shelled pea and bean (except soybean), foliage of legume vegetables (except soybean); (CG 6C and 7A), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239644	2012, BYI 02960 200 SL and BYI 02960 480 FS - Magnitude of the residue in/on soybeans, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239645	2012, BYI 02960 200 SL - Magnitude of the residue in/on fruiting vegetables (CG 8); US / Canada import tolerance, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2

PMRA Document Number	Reference
2239681	2012, BYI 02960 200 SL - Magnitude of the residue in/on cucurbit vegetables (crop group 9), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239685	2012, BYI 02960 200 SL - Magnitude of the residue in/on citrus (crop group 10), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239686	2012, BYI 02960 200 SL - Magnitude of the residue in/on pome fruits (crop group 11), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239687	2012, BYI 02960: Magnitude of the residue on blueberry, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239688	2012, BYI 02960 200 SL - Magnitude of the residue in/on small fruit vine climbing (except Fuzzy kiwifruit) Crop Subgroup 13-07F, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239689	2012, BYI 02960 200 SL - Magnitude of the residue in/on low growing berry (crop subgroup 13-07G) - strawberry, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239691	2012, BYI 02960 200 SL - Magnitude of the residue in/on tree nuts (Crop Group 14), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239692	2012, BYI 02960 200 SL and BYI 02960 480 FS - Magnitude of the residue in/on corn, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239695	2012, BYI 02960 200 SL and BYI 02960 480 FS - Magnitude of the residue in/on barley, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239696	2012, BYI 02960 200 SL and BYI 02960 480 FS - Magnitude of the residue in/on sorghum, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239698	2012, BYI 02960 200 SL and BYI 02960 480 FS - Magnitude of the residue in/on wheat, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239699	2012, BYI 02960 200 SL and BYI 02960 480 FS - Magnitude of the residue in/on cotton (Crop Subgroup 20C), DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239703	2012, BYI 02960 200 SL - Magnitude of the residue in alfalfa, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239705	2012, BYI 02960 200 SL - Magnitude of the residue in/on coffee; U.S., Canada and E.U. import tolerance, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239706	2012, BYI 02960 200 SL - Magnitude of the residue in/on hops, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239707	2012, BYI 02960 200 SL - Magnitude of the residue in peanut, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239708	2012, BYI 02960: Magnitude of the residue on prickly pear cactus, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.2
2239735	2012, Amendment 01 to the final report - Determination of residues of BYI 02960 and its metabolites, in coffee after drench application at the base of the plants, followed by foliar application of BYI 02960 (200 SL) in field trials in Brazil, DACO: 7.4.1,7.4.2,7.4.6, IIA 6.3.4
2239740	2012, Determination of the residues of BYI 02960 in/on apple and the processed fractions (whole fruit, washed; washings; raw sauce; strain rest; sauce; pomace, wet; pomace, dried; raw juice; juice, retentate; peel; fruit peeled; fruit, dried) after spraying of BYI 02960 SL 200 in the field in Germany and Belgium, DACO: 7.4.5, IIA 6.5.4
2239742	2012, BYI 02960 200 SL - Magnitude of the residue in/on processed commodities for coffee; U.S., Canada and E.U. import tolerance, DACO: 7.4.5, IIA 6.5.4
2239745	2012, BYI 02960 200 SL - Magnitude of the residue in/on field corn processed commodities, DACO: 7.4.5, IIA 6.5.4



PMRA Document Number	Reference
2239747	2012, BYI 02960 200 SL - Magnitude of the residue in cotton processed commodities (crop subgroup 20C), DACO: 7.4.5, IIA 6.5.4
2239748	2012, Determination of the residues of BYI 02960 in/on grape and the processed fractions (pomace, grape; must; wine at bottling; wine at first taste test, juice, pasteurised; jelly; washings; raisin waste; raisin) after spraying of BYI 02960 SL 200 in the field in Germany, DACO: 7.4.5, IIA 6.5.4
2239749	2012, BYI 02960 200 SL - Magnitude of the residue in/on orange processed commodities, DACO: 7.4.5, IIA 6.5.4
2239750	2012, BYI 02960 200 SL - Magnitude of the residue in/on peanut processed commodities, DACO: 7.4.5, IIA 6.5.4
2239751	2012, BYI 02960 200 SL - Magnitude of the residue in/on potato processed commodities, DACO: 7.4.5, IIA 6.5.4
2239752	2012, BYI 02960 200 SL - Magnitude of the residue in/on soybean processed commodities, DACO: 7.4.5, IIA 6.5.4
2239753	2012, Determination of the residues of BYI 02960 in/on tomato and the processed fractions (whole fruit, washed; washings; strain rest; raw juice; juice; raw puree; puree; paste; peel; peeling water; fruit peeled; preserve and tomato, dried) after spraying of BYI 02960 SL 200 in the field in southern France, Italy, Spain and Portugal, of BYI 02960 SL 200 in the field in southern France, Italy, Spain and Portugal, DACO: 7.4.5, IIA 6.5.4
2239754	2012, BYI 02960 200 SL - Magnitude of the residue in/on wheat processed commodities, DACO: 7.4.5, IIA 6.5.4
2239756	2012, Determination of the residues of BYI 02960 in/on hop (cone, green and cone, kiln-dried) and the processed fractions (hops draff, brewer's yeast and beer) after spraying of BYI 02960 SL 200 in the field in Germany, DACO: 7.4.5, IIA 6.5.4

### 3.0 Environment

PMRA Document Number	Reference
2239095	2011. BYI-02960: Hydrolytic degradation. DACO 8.2.3.2
2239100	2012. Phototransformation of [ <sup>14</sup> C]BYI 02960 in aqueous pH 7 buffer - amended report. DACO 8.2.3.3, 8.2.3.3.2
2239479	2011. [Pyridinylmethyl- <sup>14</sup> C]BYI 02960 and [furanone-4- <sup>14</sup> C]BYI 02960: Phototransformation on soil. DACO 8.2.3.3.1
2239102	2011. Phototransformation of [ <sup>14</sup> C]BYI 02960 in natural water. DACO 8.2.3.3.2
2239160	2010. BYI 02960: Calculation of the chemical half-life in the troposphere. DACO 8.2.3.3.3
2239344	2011. [Pyridinylmethyl- <sup>14</sup> C]BYI 02960: Aerobic soil metabolism/degradation and time-dependent sorption in soils. DACO 8.2.3.4.2, 8.2.4.2
2239357	2011. [Ethyl-1- <sup>14</sup> C]BYI 02960: Aerobic soil metabolism. DACO 8.2.3.4.2
2239358	2012. [Furanone-4- <sup>14</sup> C]BYI 02960: Aerobic soil metabolism in two US soils. DACO 8.2.3.4.2
2239360	2011. [Pyridine-2,6- <sup>14</sup> C]BYI 02960: Aerobic soil metabolism. DACO 8.2.3.4.2



PMRA Document Number	Reference
2239361	2011. [Furanone-4- <sup>14</sup> C]BYI 02960: Aerobic soil metabolism/degradation. DACO 8.2.3.4.2
2239366	2012. BYI 02960 - Rate of degradation of [pyridine-2,6- <sup>14</sup> C]-BYI 02960 in Brazilian soils. DACO 8.2.3.4.2
2239359	2012. [Pyridine-2,6- <sup>14</sup> C]BYI 02960: Aerobic soil metabolism in two US soils. DACO 8.2.3.4.2
2239452	2012. [Furanone-4- <sup>14</sup> C] and [Ethyl-1- <sup>14</sup> C] and [Pyridine-2,6- <sup>14</sup> C]BYI 02960: Anaerobic Soil Metabolism. DACO 8.2.3.4.4
2239453	2012. [Pyridine-2,6- <sup>14</sup> C]BYI 02960: Anaerobic soil metabolism. DACO 8.2.3.4.4
2239454	2012. [Pyridine-2,6- <sup>14</sup> C]BYI 02960: Anaerobic soil metabolism in Springfield, Nebraska (USA) soil. DACO 8.2.3.4.4
2239448	2012. [Pyridine-2,6- <sup>14</sup> C]BYI 02960: Anaerobic aquatic metabolism in two water/sediment systems. DACO 8.2.3.5.5, 8.2.3.5.6
2239486	2012. [Pyridine-2,6- <sup>14</sup> C]BYI 02960: Aerobic aquatic metabolism. DACO 8.2.3.6
2239487	2012. [1- <sup>14</sup> C]BYI 02960-DFA (BCS-AB60481): Aerobic aquatic degradation. DACO 8.2.3.6
2239488	2012. [Furanone-4- <sup>14</sup> C] and [ethyl-1- <sup>14</sup> C]BYI 02960: Aerobic aquatic metabolism. DACO 8.2.3.6
2239489	2012. Fate of BYI 02960 (tech.) in outdoor microcosm ponds simulating actual exposure conditions in agricultural use. DACO 8.2.3.6
2239342	2010. [Pyridinylmethyl- <sup>14</sup> C]BYI 02960: Adsorption/desorption on two soils. DACO 8.2.4.2
2239343	2008. [Pyridinylmethyl- <sup>14</sup> C]BYI 02960: Adsorption to and desorption from soils. DACO 8.2.4.2
2239345	2012. Amendment no 001 to final report - Adsorption / desorption of [pyridine-2,6- <sup>14</sup> C]-BYI 02960 in Brazilian soils. DACO 8.2.4.2
2239449	2011. [1- <sup>14</sup> C]BYI 02960-DFA (BCS-AB60481): Adsorption to and desorption from five soils. DACO 8.2.4.2
2239476	2012. Amendment no 001 to final report - Mobility of [Pyridine-2,6- <sup>14</sup> C]-BYI 02960 in Brazilian soils - Soil columns leaching method. DACO 8.2.4.3.1, 8.2.4.3.2
2239347	2012. Terrestrial field dissipation of BYI 02960 in Idaho soil. DACO 8.3.2
2239348	2012. Terrestrial field dissipation of BYI 02960 in California soil. DACO 8.3.2
2239350	2012. Terrestrial field dissipation of BYI 02960 in Florida soil. DACO 8.3.2
2239354	2012. Terrestrial field dissipation of BYI 02960 200 SL in three Canadian soils. DACO 8.3.2
2239356	2011. Determination of the residues of BYI 02960 in/on soil after spraying of BYI 02960 SL 200 in the field in Germany, Italy, Spain and the United Kingdom. DACO 8.3.2
2239274	2010. BYI 02960 (tech.): Acute toxicity to earthworms ( <i>Eisenia fetida</i> ) tested in artificial soil. DACO 9.2.3.1
2239279	2010. BYI 02960-difluoroacetic acid: acute toxicity to earthworms ( <i>Eisenia fetida</i> ) tested in artificial soil. DACO 9.2.3.1

PMRA Document Number	Reference
2239406	2010. BYI 02960 Difluoroacetic acid: Effects on survival, growth and reproduction on the earthworm <i>Eisenia fetida</i> tested in artificial soil with 10 % peat. DACO 9.2.3.1
2239407	2010. BYI 02960 SL 200 G: Effects on survival, growth and reproduction on the earthworm <i>Eisenia fetida</i> tested in artificial soil. DACO 9.2.3.1
2239408	2012. 6-chloronicotinic acid (AE F161089): Effects on survival, growth and reproduction on the earthworm <i>Eisenia fetida</i> tested in artificial soil with 5 percent peat. DACO 9.2.3.1
2239490	2011. BYI 02960 200 SL: A foliage residue toxicity study with the honeybee. DACO 9.2.4.1
2239281	2010. Effects of BYI 02960 - difluoroethyl - amino - furanone (acute contact and oral) on honey bees ( <i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.2
2239282	2010. Effects of 6-chloronicotinic acid (acute contact and oral) on honey bees ( <i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.2
2239284	2012. Effects of difluoroacetic acid (acute contact and oral) on honey bees ( <i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.2
2239285	2012. Effects of 6-chloro-picolyl alcohol (acute contact and oral) on honey bees ( <i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.2
2239287	2012. Revised final report no.: 1 - Effects of BYI 02960 (acute contact and oral) on honey bees ( <i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.2
2239288	2012. Effects of BYI 02960 - hydroxy (acute contact and oral) on honey bees ( <i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.2
2239605	2009. Acute toxicity of BYI 02960 to <i>Daphnia magna</i> under static conditions. DACO 9.3.2
2239607	2012. Acute toxicity of BCS-AB60481 to the waterflea <i>Daphnia magna</i> in a static laboratory test system - limit test-. DACO 9.3.2
2239598	2011. Effects of BYI 02960 (techn.) on development and reproductive output of the waterflea <i>Daphnia magna</i> in a static-renewal laboratory test system. DACO 9.3.3
2239604	2012. Influence of BYI 02960-succinamide (tech.) on development and reproductive output of the waterflea <i>Daphnia magna</i> in a static-renewal laboratory test system. DACO 9.3.3
2239259	2012. 6-chloronicotinic acid - Assessment of chronic effects to the honey bee, <i>Apis mellifera</i> L., in a 10 days continuous laboratory feeding limit test. DACO 9.3.4, 9.6.6, 9.9
2239260	2012. 6-chloropicolyl alcohol - Assessment of chronic effects to the honey bee, <i>Apis mellifera</i> L., in a 10 days continuous laboratory feeding limit test. DACO 9.3.4, 9.6.6, 9.9
2239262	2012. BYI 02960-difluoroethyl-amino-furanone (BYI 02960-DFEAF) - Assessment of chronic effects to the honey bee, <i>Apis mellifera</i> L., in a 10 days continuous laboratory feeding limit test. DACO 9.3.4, 9.6.6, 9.9
2239263	2012. BYI 02960-hydroxy - Assessment of chronic effects to the honey bee, <i>Apis mellifera</i> L., in a 10 days continuous laboratory feeding limit test. DACO 9.3.4, 9.6.6, 9.9
2239264	2012. BYI 02960 - Assessment of chronic effects to the honey bee, <i>Apis mellifera</i> L., in a 10 days laboratory feeding test. DACO 9.3.4, 9.6.6, 9.9

PMRA Document Number	Reference
2239265	2012. BYI 02960 tech.: Effects of exposure to spiked diet on honeybee larvae ( <i>Apis mellifera carnica</i> ) in an in vitro laboratory testing design. DACO 9.3.4, 9.6.6, 9.9
2239266	2012. Difluoroacetic acid - Assessment of chronic effects to the honey bee, <i>Apis mellifera L.</i> , in a 10 days continuous laboratory feeding limit test. DACO 9.3.4, 9.6.6, 9.9
2239290	2011. Acute toxicity of BYI 02960 (tech.) to larvae of <i>Chironomus riparius</i> in a 48 h static laboratory test system. DACO 9.3.4, 9.9
2239409	2012. <i>Chironomus riparius</i> 28-day chronic toxicity test with BYI 02960 (tech.) in a water-sediment system using spiked water. DACO 9.3.4, 9.9
2239611	2012. Acute toxicity of 6-chloronicotinic acid (a metabolite of imidacloprid) to <i>Chironomus tentans</i> under static renewal conditions. DACO 9.3.4
2239612	2011. Acute toxicity of BYI 02960-succinamide to larvae of <i>Chironomus riparius</i> in a 48 h static laboratory test system. DACO 9.3.4
2239613	2012. Acute toxicity of BYI 02960-azabicyclosuccinamide (BCS-CS64875) to larvae of <i>Chironomus riparius</i> in a 48 h static laboratory test system. DACO 9.3.4
2239609	2011. <i>Chironomus riparius</i> 28-day chronic toxicity test with Sodium difluoroacetate in a water-sediment system using spiked water - limit test. DACO 9.3.4
2239610	2011. <i>Chironomus riparius</i> 28-day chronic toxicity test with 6-Chloronicotinic acid in a water-sediment system using spiked water - limit test. DACO 9.3.4
2239268	2009. Acute toxicity of BYI 02960 technical to the sheepshead minnow ( <i>Cyprinodon variegatus</i> ) under static conditions. DACO 9.4.2, 9.4.3, 9.4.4
2239269	2009. BYI 02960: A 96-hour shell deposition test with the eastern oyster ( <i>Crassostrea virginica</i> ). DACO 9.4.2, 9.4.3, 9.4.4
2239270	2009. BYI 02960: A 96-hour static acute toxicity test with the saltwater mysid ( <i>Americamysis bahia</i> ). DACO 9.4.2, 9.4.3, 9.4.4
2239271	2011. BYI 02960: A flow-through life-cycle toxicity test with the saltwater mysid ( <i>Americamysis bahia</i> ). DACO 9.4.2, 9.4.3, 9.4.4
2239595	2010. Acute toxicity of BYI 02960 technical to the rainbow trout ( <i>Oncorhynchus mykiss</i> ) under static conditions. DACO 9.5.2.1, 9.5.2.3
2239596	2011. Acute toxicity of BYI 02960 to <i>Xenopus laevis</i> under flow-through conditions. DACO 9.5.2.1, 9.5.2.3
2239614	2010. Acute toxicity of BYI 02960 technical to the fathead minnow ( <i>Pimephales promelas</i> ) under static conditions. DACO 9.5.2.2, 9.5.2.3
2239615	2011. Acute toxicity of BYI 02960 (tech.) to fish ( <i>Cyprinus carpio</i> ) under static conditions (limit test). DACO 9.5.2.2, 9.5.2.3
2239616	2011. Acute toxicity of sodium difluoro acetate (BCS AB60481, tech.) to fish ( <i>Oncorhynchus mykiss</i> ) under static conditions (limit test). DACO 9.5.2.3, 9.5.2.4
2239617	2011. Acute toxicity of BYI 02960 succinamide (tech.) to fish ( <i>Oncorhynchus mykiss</i> ) under static conditions (limit test). DACO 9.5.2.3, 9.5.2.4
2239516	2011. Early life stage toxicity of BYI 02960 technical to the Fathead minnow ( <i>Pimephales promelas</i> ) under flow-through conditions. DACO 9.5.3.1
2239517	2011. Early life stage toxicity of BYI 02960 technical to the Fathead minnow ( <i>Pimephales promelas</i> ) under flow-through conditions. DACO 9.5.3.1



PMRA Document Number	Reference
2239292	2010. Toxicity of BYI 02960 technical during an acute oral LD <sub>50</sub> with the northern bobwhite quail ( <i>Colinus virginianus</i> ). DACO 9.6.2.1, 9.6.2.2, 9.6.2.3
2239293	2011. Toxicity of BYI 02960 technical during an acute oral LD <sub>50</sub> with the canary ( <i>Serinus canaria</i> ). DACO 9.6.2.1, 9.6.2.2, 9.6.2.3
2239294	2011. Acute oral toxicity of chicken ( <i>Gallus gallus domesticus</i> ) with BYI 2960 (tech.), according to OECD 223 - limit test-. DACO 9.6.2.1, 9.6.2.2, 9.6.2.3
2239410	2010. Toxicity of BYI 02960 technical during an acute dietary LC <sub>50</sub> with the mallard duck ( <i>Anas platyrhynchos</i> ). DACO 9.6.2.4, 9.6.2.5
2239411	2010. Toxicity of BYI 02960 technical during an acute dietary LC <sub>50</sub> with the northern bobwhite quail ( <i>Colinus virginianus</i> ). DACO 9.6.2.4, 9.6.2.5
2239518	2012. Toxicity of BYI 02960 technical on reproduction to the mallard duck ( <i>Anas platyrhynchos</i> ). DACO 9.6.3.1, 9.6.3.2, 9.6.3.3
2239520	2012. Toxicity of BYI 02960 technical on reproduction to the northern bobwhite quail ( <i>Colinus virginianus</i> ). DACO 9.6.3.1, 9.6.3.2, 9.6.3.3
2239404	2012. Honey bee colony feeding study, evaluating the effects of BYI 02960-fortified sugar- and pollen diet on the development of honey bee colonies under confined semi-field conditions, followed by a post-exposure field observation period. DACO 9.6.6, 9.9
2239076	2010. Toxicity of BYI 02960 technical to the green alga <i>Pseudokirchneriella subcapitata</i> . DACO 9.8.2, 9.8.3
2239077	2012. <i>Pseudokirchneriella subcapitata</i> growth inhibition test with BCS-AB60481 - limit test. DACO 9.8.2, 9.8.3
2239078	2011. <i>Pseudokirchneriella subcapitata</i> growth inhibition test with BYI 02960 - succinamide - limit test. DACO 9.8.2, 9.8.3
2239080	2012. <i>Pseudokirchneriella subcapitata</i> growth inhibition test with 6 - chloronicotinic acid. DACO 9.8.2, 9.8.3
2239162	2010. BYI 02960 SL 200 g/L - Effects on the seedling emergence and growth of eleven species of non-target terrestrial plants (Tier 1). DACO 9.8.4
2239163	2010. BYI 02960 SL 200 g/L - Effects on the seedling emergence and growth of eleven species of non-target terrestrial plants (Tier 1). DACO 9.8.4
2239164	2010. BYI 02960 SL 200 g/L - Effects on the vegetative vigour of eleven species of non-target terrestrial plants (Tier 1). DACO 9.8.4
2239165	2010. BYI 02960 SL 200 g/L - Effects on the vegetative vigour of eleven species of non-target terrestrial plants (Tier 1). DACO 9.8.4
2239096	2010. Toxicity of BYI 02960 technical to duckweed ( <i>Lemna gibba</i> G3) under static-renewal conditions. DACO 9.8.5
2239185	2009. BYI 02960 SL 200 G: Influence on mortality and reproduction on the soil mite species <i>Hypoaspis aculeifer</i> tested in artificial soil with 5 % peat. DACO 9.9
2239217	2011. 6-chloronicotinic acid (AE F161089): Influence on mortality and reproduction on the soil mite species <i>Hypoaspis aculeifer</i> tested in artificial soil. DACO 9.9
2239218	2012. Metabolite BYI 02960-difluoroacetic acid: Influence on the reproduction of the collembolan species <i>Folsomia candida</i> tested in artificial soil. DACO 9.9
2239219	2010. BYI 02960-DFA (BCS-AA56716): Influence on mortality and reproduction on the soil mite species <i>Hypoaspis aculeifer</i> tested in artificial soil with 5 % peat. DACO 9.9



PMRA Document Number	Reference
2239220	2012. 6-chloronicotinic acid (AE F161089): Influence on the reproduction of the collembolan species <i>Folsomia candida</i> tested in artificial soil. DACO 9.9
2239237	2012. Technical grade BYF 02960: A two-generation reproductive toxicity study in the Wistar rat. DACO 4.5.1, 5.6.1
2239256	2012. BYI 02960 - Acute toxicity in the rat after oral administration. DACO 4.2.1, 5.2.1
2239450	2012. Soil adsorption/desorption study 6-chloronicotinic acid (Acetamiprid metabolite). DACO 8.2.4.2
2239478	2012. Rate of degradation of the acid metabolite, ( <sup>14</sup> C)-IC-O in three soils NI-25. DACO 8.2.3.4.2
2239280	2012. Acute toxicity to earthworms ( <i>Eisenia foetida</i> ) IC-0. DACO 9.2.3.1
2239606	2012. Acute toxicity (48 hours) to Daphnids ( <i>Daphnia magna</i> ) under semi-static conditions IC-0. DACO 9.3.2
2236542	2011. Effects of BYI 02960 FS 480 G (acute contact and oral) on honey bees ( <i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.8
2236537	2012. A field study to determine residues of BYI 02960 in guttation liquid from winter oil-seed rape (OSR) plants in Northern Germany in 2010/2011. DACO 9.2.9
2236539	2012. A field study to determine residues of BYI 02960 in guttation liquid from winter oil-seed rape (OSR) plants in France in 2010/2011. DACO 9.2.9
2236691	2012. Revised final report no.: 1 - Effects of BYI 02960 SL 200 G (acute contact and oral) on honey bees ( <i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.8
2236692	2010. Effects of a test item mix of BYI 02960 SL 200 G + tebuconazole EW 250C G (acute contact and oral) on honey bees ( <i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.8
2236656	2012. Determination of residues of BYI 02960 applied via drench application in watermelon in the semi-field. DACO 9.2.8
2236658	2012. Determination of residues of BYI 02960 applied via drench application in tomato in the semi-field. DACO 9.2.8
2236659	2012. Determination of residues of BYI 02960 in blossoms, nectar, and pollen when applied via Foliar Spray to early blooming citrus under semi-field conditions in Florida. DACO 9.2.8
2236660	2012. Determination of residues of BYI 02960 in blossoms, nectar, and pollen when applied via soil drench and Foliar Spray to melon under semi-field Conditions in North Carolina. DACO 9.2.8
2236661	2012. Determination of residues of BYI 02960 applied via drench application in watermelon in the semi-field. DACO 9.2.8
2236662	2012. BYI 02960 200 SL - Magnitude of the residue in bee food items, cotton. DACO 9.2.8
2236664	2012. BYI 02960 200 SL - Magnitude of the residue in/on bee relevant blueberry matrices. DACO 9.2.8
2236665	2012. Determination of residues of BYI 02960 in blossoms, nectar, and pollen when applied via foliar spray to early blooming apple under semi-field conditions in North Carolina. DACO 9.2.8
2236666	2012. BYI 02960 200 SL - Magnitude of the residue in/on bee relevant apple matrices. DACO 9.2.8

PMRA Document Number	Reference
2236684	2012. BYI 02960 SL 200 G: A semi-field study in Denmark 2010 to evaluate effects of spray applications in <i>Phacelia tanacetifolia</i> on the honeybee <i>Apis mellifera</i> L. (Hymenoptera, Apidae). DACO 9.2.8
2236685	2012. BYI 02960 SL 200 G: A semi-field study in Italy 2011 to evaluate effects of spray applications in <i>Phacelia tanacetifolia</i> on the honeybee <i>Apis mellifera</i> L. (Hymenoptera, Apidae). DACO 9.2.8
2236686	2012. BYI 02960 SL 200 G: A semi-field study in Germany 2009 to evaluate effects of spray applications in <i>Phacelia tanacetifolia</i> on the honeybee <i>Apis mellifera</i> L. (Hymenoptera, Apidae). DACO 9.2.8
2236687	2012. Evaluation of the effects of BYI 02960 SL 100 on honey bees ( <i>Apis mellifera</i> ) in a semifield tunnel test in full-flowering <i>Phacelia tanacetifolia</i> . DACO 9.2.8
2236688	2012. Evaluation of the effects of BYI 02960 SL 200 on honey bees ( <i>Apis mellifera</i> ) in a semifield tunnel test in full-flowering <i>Phacelia tanacetifolia</i> . DACO 9.2.8
2236689	2012. Determination of side-effects of BYI 02960 SL 200 G on honey bee ( <i>Apis mellifera</i> L.) brood under semi-field conditions. DACO 9.2.8
2236638	2010. Toxicity to the predatory mite <i>Typhlodromus pyri</i> SCHEUTEN (Acari, Phytoseiidae) using a laboratory test; BYI 02960 SL 200 g/L. DACO 9.2.8
2236639	2010. Toxicity to the parasitoid wasp <i>Aphidius rhopalosiphi</i> (DESTEPHANI-PEREZ) (Hymenoptera: Braconidae) using a laboratory test; BYI 02960 SL 200 g/L. DACO 9.2.8
2236645	2010. Toxicity to the predatory mite <i>Typhlodromus pyri</i> SCHEUTEN (Acari, Phytoseiidae) using an extended laboratory test on <i>Phaseolus vulgaris</i> BYI 02960 SL 200 (g/L). DACO 9.2.8
2236646	2010. Toxicity to the parasitoid wasp <i>Aphidius rhopalosiphi</i> (DESTEPHANI-PEREZ) (Hymenoptera: Braconidae) using an extended laboratory test on barley BYI 02960 SL 200 (g/L). DACO 9.2.8
2236647	2010. Chronic toxicity (ER50) of BYI 02960 SL 200 (g/L) to the rove beetle <i>Aleochara bilineata</i> Gyll. (Coleoptera: Staphylinidae) under extended laboratory conditions. DACO 9.2.8
2236648	2010. Toxicity to the ladybird beetle <i>Coccinella septempunctata</i> L. (Coleoptera, Coccinellidae) using an extended laboratory test on <i>Phaseolus vulgaris</i> ; BYI 02960 SL 200 (g/L). DACO 9.2.8
2236644	2010. BYI 02960 SL 200 G: acute toxicity to earthworms ( <i>Eisenia fetida</i> ) tested in artificial soil with 5 percent peat. DACO 9.2.8
2236681	2009. BYI 02960 SL 200 G: Influence on the reproduction of the collembola species <i>Folsomia candida</i> tested in artificial soil with 5 % peat. DACO 9.2.8
2236673	2012. Assessment of side effects on the honeybee ( <i>Apis mellifera</i> L.), exposed to winter oil-seed rape, grown from seeds treated with BYI 02960 FS 480 G and sequentially sprayed with BYI 02960 SL 200 G during immediate pre- and full flowering in a long-term field study in Northern Germany. DACO 9.2.9
2236675	2012. Assessment of side effects on the honeybee ( <i>Apis mellifera</i> L.), exposed to winter oil-seed rape, grown from seeds treated with BYI 02960 FS 480 G and sequentially sprayed with BYI 02960 SL 200 G during immediate pre- and full flowering in a long-term field study in France. DACO 9.2.9
2236653	2010. Toxicity to the parasitoid wasp <i>Aphidius rhopalosiphi</i> (DESTEPHANI-PEREZ) (Hymenoptera: Braconidae) in an extended laboratory test (under semi-field conditions aged residues on <i>Zea mays</i> ) BYI 02960 SL 200 (g/L). DACO 9.2.9

PMRA Document Number	Reference
2236654	2010. Effects of BYI 02960 SL 200 (g/L) on the predatory bug <i>Orius laevis</i> extended laboratory study - aged residue test. DACO 9.2.9
2236670	2012. A field study to assess the effects of BYI 02960 (SL 200 g/L) on the non-target, surface- and plant-dwelling arthropod fauna of a grassland habitat (off-crop) in SW France during summer. DACO 9.2.9
2236672	2012. A field study to assess the effects of BYI 02960 SL 200 g/L on the non-target, surface- and plantdwelling, arthropod fauna of a grassland habitat (off-crop) in The Netherlands during summer. DACO 9.2.9
2236669	2012. BYI 02960 SL 200 G: Effects on the earthworm fauna of a grassland area within one year. DACO 9.2.9
2236701	2010. Acute toxicity of BYI 02960 SL 200 G to the waterflea <i>Daphnia magna</i> in a static laboratory test system. DACO 9.3.2
2236700	2011. Chironomus riparius 28-day chronic toxicity test with BYI 02960 SL 200 G in a water-sediment system using spiked water. DACO 9.3.5
2236693	2012. Acute toxicity of BYI 02960 SL 200 G to fish ( <i>Oncorhynchus mykiss</i> ) under static conditions-limit test. DACO 9.5.4
2236694	2011. Acute toxicity of BYI 02960 SL 200 G to fish ( <i>Cyprinus carpio</i> ) under static conditions (limit test). DACO 9.5.4
2236682	2012. Toxicity of BYI 02960 sl 200 during an acute oral LD50 with the Northern bobwhite quail ( <i>Colinus virginianus</i> ). DACO 9.6.4
2236683	2012. Acute oral toxicity of chicken ( <i>Gallus gallus domesticus</i> ) with BYI 02960 SL 200, according to OECD 223 - limit test-. DACO 9.6.4
2236667	2012. Statement on residue dissipation of flupyradifurone in treated foliage of lettuce and spinach: kinetic evaluation of US data. DACO 9.7.2
2236702	2010. <i>Pseudokirchneriella subcapitata</i> growth inhibition test with BYI 02960 SL 200 G. DACO 9.8.2
2236695	2010. BYI 02960 SL 200 g/L - Effects on the vegetative vigour of eleven species of non-target terrestrial plants (Tier 1). DACO 9.8.6
2236696	2010. BYI 02960 SL 200 g/L - Effects on the vegetative vigour of eleven species of non-target terrestrial plants (Tier 1). DACO 9.8.6
2236710	2010. BYI 02960 SL 200 g/L - Effects on the seedling emergence and growth of eleven species of non-target terrestrial plants (Tier 1). DACO 9.8.6
2239347	2012. Terrestrial field dissipation of BYI 02960 in Idaho soil. DACO 8.3.2
2239348	2012. Terrestrial field dissipation of BYI 02960 in California soil. DACO 8.3.2
2239350	2012. Terrestrial field dissipation of BYI 02960 in Florida soil. DACO 8.3.2
2239354	2012. Terrestrial field dissipation of BYI 02960 200 SL in three Canadian soils. DACO 8.3.2
2239356	2011. Determination of the residues of BYI 02960 in/on soil after spraying of BYI 02960 SL 200 in the field in Germany, Italy, Spain and the United Kingdom. DACO 8.3.2
2239346	2012. Stability of BYI 02960 and its metabolites 6-chloronicotinic acid (6-CNA) and difluoroacetic acid (DFA) in soil during frozen storage, 2010 (reported through 381 days of storage). DACO 8.6



#### 4.0 Value

PMRA Document Number	Reference
2236524	2012, BYI 02960 480 FS - Seed treatment insecticide for soybean, DACO: 10.2.3.3, 10.2.3.4, 10.3.2, 10.5.1, 10.5.2, 10.5.4, IIIA 6.1.2, IIIA 6.1.3, IIIA 6.2.1, IIIA 6.4.1, IIIA 6.4.2, IIIA 6.4.3
2284014	2012, BYI 02960 480 FS - Seed treatment insecticide for soybean, DACO: 10.2.3.1
2284020	2012, BYI 02960 480 FS - Seed treatment insecticide for soybean, DACO: 10.2.3.1
2284021	2012, BYI 02960 480 FS - Seed treatment insecticide for soybean, DACO: 10.3.1
2284022	2012, BYI 02960 480 FS - Seed treatment insecticide for soybean, DACO: 10.3.1
2236630	2012, Flupyradifurone SL 200 1X1000L IBC WW, DACO: 10.6.3.7, IIIA 1.7
2236625	2012, Sivanto 200 SL - Insecticide for insect control in horticultural crops - Data to support drench and drip irrigation treatments, DACO: 10.2.3.3, 10.2.3.4, 10.3.2, 10.5.1, 10.5.2, 10.5.4, IIIA 6.1.2, IIIA 6.1.3, IIIA 6.2.1, IIIA 6.4.1, IIIA 6.4.2, IIIA 6.4.3
2236627	2012, Sivanto 200 SL - Insecticide for control of insect pests in fruit, vegetable and field crops - Data to support foliar applications, DACO: 10.2.3.3, 10.2.3.4, 10.3.2, 10.5.1, 10.5.2, 10.5.4, IIIA 6.1.2, IIIA 6.1.3, IIIA 6.2.1, IIIA 6.4.1, IIIA 6.4.2, IIIA 6.4.3
2236633	2013, Bayer CropScience (BCS) Response To Completeness Check Clarifications/Deficiencies Related To Global Joint Review Submissions Of Flupyradifurone Technical, Sivanto 200 SL & BYI 02960 480 FS, DACO: 10.2.3.1, 10.2.3.3, 2.11.2.2, 11.4.2, 13.2.2, 13.4.4, 2.6, 4.3, 6.4.5, 12.4.5, 13.5, 14.5, 9, 7.3, 7.4.4 CBI
2236634	2012, Tier 2 summary of the the efficacy data and value information of the plant production product Sivanto 200 SL for drench and drip application, DACO: 12.7, Document M
2284002	2012, Tier 2 summary of the the efficacy data and value information of the plant production product Sivanto 200 SL for foliar spray application, DACO: 12.7, Document M

#### B. Additional Information Considered

##### i) Published Information

#### 1.0 Value

PMRA Document Number	Reference
2444721	University of Florida. Accessed April 23, 2012. Whiteflies. Entomology and Nematology. <a href="http://nfrec.ifas.ufl.edu/MizellRF/WoodyBug/whitefly.htm">http://nfrec.ifas.ufl.edu/MizellRF/WoodyBug/whitefly.htm</a> . DACO 10.6
2444723	Michigan State University. Accessed April 22, 2014. Arthropod Pesticide Resistance Database. <a href="http://www.pesticideresistance.org/index.php">http://www.pesticideresistance.org/index.php</a> . DACO 10.6



## 2.0 Environment

PMRA Document Number	Reference
1573006	Atkins E.L., Kellum D., and Atkins K.W. 1981. Reducing Pesticide Hazards to Honey Bees: Mortality prediction techniques and integrated management strategies. Univ. Calif., Div. Agric. Sci. Leaflet 2883.
1918520	Cohen, S.Z., Creeger, S.M., Carsel, R.F., Enfield, C.G. 1984. Potential for pesticide contamination of groundwater resulting from agricultural uses. In: Krueger, R. F. And J.N. Seiber (eds.), Treatment and Disposal of Pesticide Wastes. Am. Chem. Soc., Washington, DC. ACS Symp. Ser. 259. pp. 297-325.
2439880	Crailsheim, K., Schneider, L.H.W, Hrassnigg, N., Bühlmann, G., Brosch, U.; Gmeinbauer, R., and B. Schöffmann. 1992. Pollen consumption and utilization in worker honeybees ( <i>Apis mellifera carnica</i> ): dependence on individual age and function. J. Insect Physiol., 38 (6): 409-419.
2439881	Crailsheim, K.; Hrassnigg, N.; Gmeinbauer, R.; Szolderits, M.J.; Schneider, L.H.W. and U. Brosch. 1993. Pollen utilization in non-breeding honeybees in winter. J. Insect Physiol. 39 (5): 369-373.
1918522	Fletcher JS; Nellessen JE; Pfleeger TG. 1994. Literature review and evaluation of the EPA food chain (Kenaga) nomogram, an instrument for estimating pesticide residues on plants. Environ. Toxicol. Chem. 13:1383 - 1391.
1918524	Gustafson, D.I. 1989. Groundwater ubiquity score: a simple method for assessing pesticide leachability. Environmental Toxicology and Chemistry, 8: 339-357.
2439884	Koch H. and Weisser P. 1997. Exposure of honey bees during pesticide application under field conditions. Apidologie, 28: 439-447.
1918529	Nagy, KA, 1978. Field metabolic rate and food requirement scaling in mammals and birds. Ecological Monograph. Vol.57, No.2, pp.111-128.
2439883	Rortais A., Arnold G., Halm M.P., and Touffet-Briens F. 2005. Modes of exposure of honeybees to systemic insecticides: estimated amounts of contaminated pollen and nectar consumed by different categories of bees. Apidologie 36: 71-83.

---

### Other References

Briggs, G., Bromilow, R., Evans, A., and Williams, M. 1983. Relationships between lipophilicity and the distribution of non-ionised chemicals in barley shoots following uptake by the roots. *Pesticide Science*, 14, 492-500.

Briggs, G., Bromilow, R., Evans, A.A. 1982. Relationships between lipophilicity and root uptake and translocation of non-ionised chemicals by barley. *Pesticide Science*, 13, 495-504.

Candolfi M.P., Barrett K.L., Campbell P., Forster R., Grandy N., Huet M.-C., Lewis G., Oomen P.A., Schmuck R., and Vogt H. 2001. Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. In SETAC/ESCORT2 Workshop Report, 21-23 March 2000, Wageningen (NL).

ICPBR Bee Protection Symposium, Wageningen, The Netherlands, 2-4 November 2011.

Linders J, Mensink, H., Stephenson G., Wauchope D., and Racke K. 2000. Foliar interception and retention values after pesticide application. A proposal for standardized values for environmental risk assessment (technical report). *Pure Appl Chem* 72 (11): 2199-2218.

USEPA, 2012. White Paper in Support of the Proposed Risk Assessment Process for Bees Submitted to the FIFRA Scientific Advisory Panel for Review and Comment September 11 – 14, 2012. [http://www.cdpr.ca.gov/docs/emon/surfwtr/presentations/epa\\_whitepaper.pdf](http://www.cdpr.ca.gov/docs/emon/surfwtr/presentations/epa_whitepaper.pdf)